Second Request

Access DB# 54344

RUSH

SEARCH REQUEST FORM

Scientific and Technical Information Center

MEJ

Requester's Full Name: Moideh Bahar Examiner #: 78209 Date: Nov. 7, 2001
Art Unit: 1617 Phone Number 305-1007 Serial Number: 09/776935
Mail Box and Bldg/Room Location: 2B19 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Inhibition of P38 kinase using aryl & heteroaryl substituted heterocyclic ureas

Inventors (please provide full names): Jacques Dumas, Uday KHIRE, Tim LOWINGER, Bernd RIEDL, William J. SCOTT, Roger A. SMITH, Jill F. WOOD, ...

Earliest Priority Filing Date: Dec 22, 1998

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search the full scope of the claims.

Claim 1

Claim 4

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Shep Pam	NA Sequence (#)	STN
Searcher Phone #: 308-4499	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed: 11/8/01	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (1-2000)

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=> s 227623-09-8/rn
             2 227623-09-8
             0 227623-09-8D
L23          2 227623-09-8/RN
                 (227623-09-8 (NOTL) 227623-09-8D )

=> d l23 1-2 AB BIB KWIC

L23  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AB   A method for treatment of p38-mediated disease other than cancer
comprises
     administration of ANHCONHB [I; A = substituted pyrazolyl, thienyl, furyl;
     B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg.
     .gtoreq.1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms].
     Reaction of 2,3-dichlorophenyl isocyanate with
1-(4-methoxyphenyl)-3-tert-
     butyl-5-aminopyrazole in toluene gave title compd. II.  In an in vitro
p38
     kinase assay, I displayed IC50 values of 1-10 .mu.M.
AN   1999:425744  CAPLUS
DN   131:73649
TI   Preparation of pyrazolyl aryl ureas and related compounds as p38 kinase
     inhibitors
IN   Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd;
Scott,
     William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia;
Johnson,
     Jeffrey; Redman, Aniko; Sibley, Robert
PA   Bayer Corporation, USA
SO   PCT Int. Appl., 56 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
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PI   WO 9932110          A1   19990701       WO 1998-US26079   19981222
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9919970          A1   19990712       AU 1999-19970     19981222
     EP 1043995          A1   20001018       EP 1998-964708    19981222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRAI US 1997-995751     A    19971222
     WO 1998-US26079    W    19981222
OS   MARPAT 131:73649
RE.CNT  1
RE
(1) Kamata; US 5319099 A 1994 CAPLUS
IT   227622-85-7P   227622-86-8P   227622-87-9P   227622-90-4P   227622-91-5P
     227622-92-6P   227622-93-7P   227622-94-8P   227622-95-9P   227622-96-0P
     227622-98-2P   227622-99-3P   227623-01-0P   227623-02-1P   227623-03-2P
     227623-04-3P   227623-05-4P   227623-06-5P   227623-08-7P
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227623-18-9P 227623-19-0P 227623-20-3P 227623-24-7P 227623-25-8P
227623-30-5P 227623-31-6P 228564-94-1P 228564-95-2P 228564-96-3P
228564-97-4P 228564-98-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazolyl aryl ureas and related compds. as p38 kinase inhibitors)

L23 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AB The title compds. ANHCONHB (A = heteroaryl; B = aryl, heteroaryl), raf kinase inhibitors, were prepd. E.g., N-(1-phenyl-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea was prepd.
AN 1999:421660 CAPLUS
DN 131:44811
TI Preparation of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors
IN Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert
PA Bayer Corporation, USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9932455	A1	19990701	WO 1998-US26082	19981222
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9919055	A1	19990712	AU 1999-19055	19981222
	EP 1056725	A1	20001206	EP 1998-963810	19981222
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2000003231	A	20000822	NO 2000-3231	20000621
PRAI	US 1997-996181	A	19971222		
	WO 1998-US26082	W	19981222		

OS MARPAT 131:44811
RE.CNT 1
RE
(1) Creswell; US 5162360 A 1992 CAPLUS
IT 227622-85-7P 227622-86-8P 227622-87-9P 227622-88-0P 227622-89-1P
227622-90-4P 227622-91-5P 227622-92-6P 227622-93-7P 227622-94-8P
227622-95-9P 227622-96-0P 227622-97-1P 227622-98-2P 227622-99-3P
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227623-18-9P 227623-19-0P 227623-20-3P 227623-21-4P 227623-22-5P
227623-23-6P 227623-24-7P 227623-25-8P 227623-30-5P 227623-31-6P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors)

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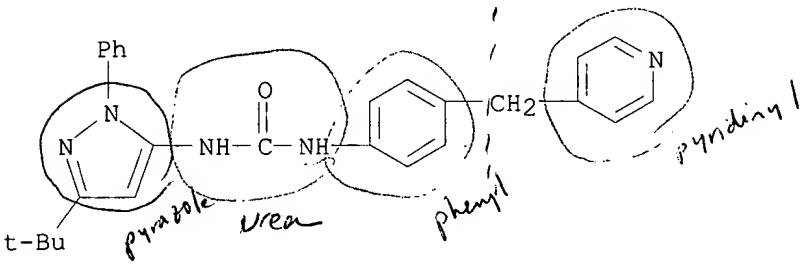
L12 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-09-8 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-phenyl-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H27 N5 O
SR CA
LC STN Files: CA, CAPLUS



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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=>  s 227623-09-8/rn
             2 227623-09-8
             0 227623-09-8D
L13          2 227623-09-8/RN
                (227623-09-8 (NOTL) 227623-09-8D )

=> d l13

L13  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AN   1999:425744  CAPLUS
DN   131:73649
TI   Preparation of pyrazolyl aryl ureas and related compounds as p38 kinase
     inhibitors
IN   Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd;
Scott,
     William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia;
Johnson,
     Jeffrey; Redman, Aniko; Sibley, Robert
PA   Bayer Corporation, USA
SO   PCT Int. Appl., 56 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
PI   WO 9932110          A1   19990701       WO 1998-US26079   19981222
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9919970          A1   19990712       AU 1999-19970     19981222
     EP 1043995          A1   20001018       EP 1998-964708    19981222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRAI US 1997-995751     A    19971222
     WO 1998-US26079    W    19981222
OS   MARPAT 131:73649
RE.CNT  1
RE
(1) Kamata; US 5319099 A 1994 CAPLUS


=> d 2

L13  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AN   1999:421660  CAPLUS
DN   131:44811
TI   Preparation of aryl- and heteroaryl-substituted heterocyclic ureas as raf
     kinase inhibitors
IN   Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger;
     Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.;
     Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert
PA   Bayer Corporation, USA
SO   PCT Int. Appl., 58 pp.
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     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND  DATE           APPLICATION NO.   DATE
     ---------------     ----  --------       ---------------   --------
PI   WO 9932455           A1   19990701       WO 1998-US26082   19981222
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9919055            A1   19990712       AU 1999-19055     19981222
     EP 1056725            A1   20001206       EP 1998-963810    19981222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     NO 2000003231         A    20000822       NO 2000-3231      20000621
PRAI US 1997-996181        A    19971222
     WO 1998-US26082       W    19981222
OS   MARPAT 131:44811
RE.CNT  1
RE
(1) Creswell; US 5162360 A 1992 CAPLUS


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L14 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2001 ACS

AB The title compds. WX1C(:Y)X2Z [W = (un)substituted satd., partially satd. or arom. monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms; Y = O, etc.; X1, X2 = O, S, etc.; Z = cycloalkyl, etc.] are prepd. Compds. of this invention are inhibitors of **p38**, a mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli. In in vitro assays for inhibition of phosphorylation of EGF receptor peptide, compds. of this invention showed IC50 values of 0.14 .mu.M to 19 .mu.M.

AN 1999:34888 CAPLUS

DN 130:66491

TI Preparation of **urea** derivatives as inhibitors of **p38**

IN Salituro, Francesco Gerald; Bemis, Guy W.; Green, Jeremy; Kofron, James L.

PA Vertex Pharmaceuticals Incorporated, USA

SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9900357	A1	19990107	WO 1998-US13496	19980629
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6093742	A	20000725	US 1997-884160	19970627
AU 9883776	A1	19990119	AU 1998-83776	19980629
EP 993441	A1	20000419	EP 1998-934195	19980629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-884160 A 19970627
WO 1998-US13496 W 19980629

OS MARPAT 130:66491

RE.CNT 5

RE

(1) Adams, J; WO 9531451 A 1995 CAPLUS
(2) Sugen Inc; WO 9640673 A 1996 CAPLUS
(3) Vertex Pharma; WO 9740028 A 1997 CAPLUS
(4) Widdowson, K; WO 9749399 A 1997 CAPLUS
(5) Widdowson, K; WO 9749400 A 1997 CAPLUS

TI Preparation of **urea** derivatives as inhibitors of **p38**

AB The title compds. WX1C(:Y)X2Z [W = (un)substituted satd., partially satd. or arom. monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms; Y = O, etc.; X1, X2 = O, S, etc.; Z = cycloalkyl, etc.] are prepd. Compds. of this invention are inhibitors of **p38**, a mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli. In in vitro assays for inhibition of phosphorylation of EGF receptor peptide, compds. of this invention showed IC50 values of 0.14 .mu.M to 19 .mu.M.

ST **p38** inhibitor **urea** prepn; **urea** prepn
p38 inhibitor

IT Neutropenia
(autoimmune; prepn. and therapeutic effect of **urea** derivs. as inhibitors of **p38**)

IT Alzheimer's disease
Edema
Graves' disease
Headache
Hypoxia (animal)
Kaposi's sarcoma
Leukemia
Melanoma
Multiple myeloma
Myocardial ischemia
Parkinson's disease
Platelet aggregation
Renal ischemia
Scleroderma
Septic shock
(prepn. and effect of **urea** derivs.)
IT Infection
Nerve degeneration
(prepn. and therapeutic effect of **urea** derivs.)
IT Adult respiratory distress syndrome
Atopic dermatitis
Bone diseases
Crohn's disease
Gastritis
Graft vs. host reaction
Hepatitis
Lupus erythematosus
Multiple sclerosis
Myasthenia gravis
Nephritis
Osteoarthritis
Osteoporosis
Pancreatitis
Psoriasis
Rheumatoid arthritis
Thrombocytopenia
Ulcerative colitis
(prepn. and therapeutic effect of **urea** derivs. as inhibitors of **p38**)
IT Ocular inflammation
Retina
(retinitis; prepn. and effect of **urea** derivs.)
IT Inflammation
Thyroid diseases
(thyroiditis; prepn. and therapeutic effect of **urea** derivs. as inhibitors of **p38**)
IT Allergy inhibitors
Analgesics
Anti-inflammatory drugs
Antiasthmatics
Antitumor agents
(**urea** derivs.)
IT Autoimmune diseases
(**urea** derivs. effect on autoimmune diseases)
IT Shigella
(**urea** derivs. effect on shigella)
IT Viral infection
(**urea** derivs. effect on viral infections)
IT 101-20-2P 369-81-3P 1566-96-7P 2008-73-3P 4300-43-0P
13114-79-9P

13141-95-2P 13142-35-3P 13142-47-7P 13142-48-8P 13142-50-2P
13143-23-2P 13208-22-5P 13256-73-0P 16655-20-2P 85260-98-6P
107917-67-9P 117745-34-3P 196617-12-6P 196617-13-7P 196700-19-3P
196700-39-7P 196700-55-7P 196700-64-8P 197800-69-4P 199741-56-5P
202598-90-1P 218134-88-4P 218134-90-8P 218134-91-9P 218134-92-0P
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218136-17-5P 218136-18-6P 218136-19-7P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **urea** derivs. as inhibitors of **p38**)

IT 97-50-7, 5-Chloro-2,4-dimethoxyaniline 103-71-9, Phenylisocyanate, reactions 134-19-0 136-95-8, 2-Aminobenzothiazole 622-58-2, 4-Methylphenylisocyanate 6358-07-2 6376-14-3, 4-Chloro-2-methoxy-5-methylaniline 59377-19-4, 4-Phenoxyphenylisocyanate
RL: RCT (Reactant)
(prepn. of **urea** derivs. as inhibitors of **p38**)

IT 26135-24-0P 218136-20-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**urea** derivs.)

IT 165245-96-5, **p38** MAP kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**urea** derivs.)

L14 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2001 ACS

AB The title **ureas** ANHC(O)NHB [I; A = (un)substituted C6-12 aryl, C5-12 heteroaryl; B = II-V; R1 = H, C1-4 alkyl; R2, R3 = halo, COOR1, CN, etc.; R5 = C3-5 alkyl], useful in treating cytokine mediated diseases other than cancer and proteolytic enzyme mediated diseases other than cancer, were prepd. Thus, reaction of N-methyl-3-amino-5-tert-butylthiophene-2-carboxamide (prepn. given) with 4-methylphenyl isocyanate
in PhMe afforded 44% the title compd. VI. Compds. I are useful in treating diseases mediated by TNF.alpha., MMP-1, MMP-3, IL-1, IL-6, or IL-8 such as **rheumatoid arthritis**, osteoporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-vs.-graft reactions. All exemplified compds. I showed **p38** IC50s of 1 nM - 10 .mu.M.

AN 1998:776671 CAPLUS

DN 130:38286

TI Inhibition of **p38** kinase activity by aryl **ureas**
IN Ranges, Gerald; Scott, William; Bombara, Michael; Rauner, Deborah; Redman,
Aniko; Smith, Roger; Paulsen, Holger; Chen, Jinshan; Gunn, David; Renick, Joel
PA Bayer Corp., USA; et al.
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9852558	A1	19981126	WO 1998-US10375	19980521
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9875854	A1	19981211	AU 1998-75854	19980521
	EP 1019040	A1	20000719	EP 1998-923600	19980521
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1997-863022	A2	19970523		
	WO 1998-US10375	W	19980521		

OS MARPAT 130:38286
RE.CNT 1
RE
(1) Tarzia, G; 1979, P594
TI Inhibition of **p38** kinase activity by aryl **ureas**
AB The title **ureas** ANHC(O)NHB [I; A = (un)substituted C6-12 aryl, C5-12 heteroaryl; B = II-V; R1 = H, C1-4 alkyl; R2, R3 = halo, COOR1, CN, etc.; R5 = C3-5 alkyl], useful in treating cytokine mediated diseases other than cancer and proteolytic enzyme mediated diseases other than cancer, were prepd. Thus, reaction of N-methyl-3-amino-5-tert-butylthiophene-2-carboxamide (prepn. given) with 4-methylphenyl isocyanate
in PhMe afforded 44% the title compd. VI. Compds. I are useful in treating diseases mediated by TNF.alpha., MMP-1, MMP-3, IL-1, IL-6, or IL-8 such as **rheumatoid arthritis**, osteoporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-vs.-graft reactions. All exemplified compds. I showed **p38** IC50s of 1 nM - 10 .mu.M.
ST **p38** kinase inhibitor aryl **urea** prepn; MMP mediated disease aryl **urea** prepn; matrix metalloproteinase mediated disease arylurea prepn; tumor necrosis factor arylurea prepn; cytokine mediated disease arylurea prepn; interleukin mediated disease arylurea prepn; antiinflammatory arylurea prepn; antiarthritic arylurea prepn; antiasthmatic arylurea prepn; antirheumatic arylurea prepn; osteoporosis arylurea prepn; septic shock arylurea prepn; inflammatory bowel disease arylurea prepn; host versus graft reaction arylurea prepn
IT Immunological diseases
Transplant (organ)
(host-vs.-graft reaction; inhibition of **p38** kinase activity by aryl **ureas**)
IT Anti-inflammatory drugs
Antiarthritics

Antiasthmatics
Antirheumatic drugs
(inhibition of **p38** kinase activity by aryl **ureas**)

IT Interleukin 1
Interleukin 6
Interleukin 8
Tumor necrosis factor .alpha.
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT Inflammatory bowel diseases
Osteoporosis
Septic shock
(treatment of; inhibition of **p38** kinase activity by aryl **ureas**)

IT 216573-01-2P 216574-43-5P
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant);
SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT 216572-93-9P 216572-95-1P 216572-97-3P 216572-99-5P 216573-03-4P
216573-05-6P 216573-07-8P 216573-09-0P 216573-11-4P 216573-13-6P
216573-15-8P 216573-16-9P 216573-17-0P 216573-18-1P 216573-19-2P
216573-20-5P 216573-21-6P 216573-22-7P 216573-23-8P 216573-24-9P
216573-25-0P 216573-26-1P 216573-27-2P 216573-28-3P 216573-29-4P
216573-30-7P 216573-31-8P 216573-32-9P 216573-33-0P 216573-34-1P
216573-35-2P 216573-36-3P 216573-37-4P 216573-38-5P 216573-40-9P
216573-42-1P 216573-43-2P 216573-45-4P 216573-47-6P 216573-48-7P
216573-49-8P 216573-50-1P 216573-51-2P 216573-52-3P 216573-53-4P
216573-54-5P 216573-55-6P 216573-56-7P 216573-57-8P 216573-58-9P
216573-59-0P 216573-60-3P 216573-61-4P 216573-62-5P 216573-63-6P
216573-64-7P 216573-65-8P 216573-66-9P 216573-67-0P 216573-68-1P
216573-69-2P 216573-70-5P 216573-71-6P 216573-72-7P 216573-73-8P
216573-74-9P 216573-75-0P 216573-76-1P 216573-77-2P 216573-78-3P
216573-79-4P 216573-80-7P 216573-81-8P 216573-82-9P 216573-83-0P
216573-84-1P 216573-85-2P 216573-86-3P 216573-87-4P 216573-88-5P
216573-89-6P 216573-90-9P 216573-91-0P 216573-92-1P 216573-93-2P
216573-94-3P 216573-95-4P 216573-96-5P 216573-97-6P 216573-98-7P
216573-99-8P 216574-00-4P 216574-01-5P 216574-02-6P 216574-03-7P
216574-04-8P 216574-05-9P 216574-06-0P 216574-07-1P 216574-08-2P
216574-09-3P 216574-10-6P 216574-11-7P 216574-12-8P 216574-13-9P
216574-14-0P 216574-15-1P 216574-16-2P 216574-17-3P 216574-18-4P
216574-19-5P 216574-20-8P 216574-21-9P 216574-22-0P 216574-23-1P
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216574-34-4P 216574-35-5P 216574-36-6P 216574-37-7P 216574-38-8P
216574-39-9P 216574-40-2P 216574-41-3P 216574-42-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT 9001-12-1, MMP-1 79955-99-0, MMP-3 165245-96-5, **p38** Kinase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT 75-97-8, Pinacolone 95-76-1, 3,4-Dichloroaniline 96-35-5, Methyl glycolate 99-98-9 103-71-9, Phenyl isocyanate, reactions 105-34-0, Methyl cyanoacetate 106-49-0, 4-Methylaniline, reactions 107-91-5, .alpha.-Cyanoacetamide 108-44-1, 3-Methylaniline, reactions 371-40-4,

4-Fluoroaniline 507-20-0, 2-Chloro-2-methylpropane 616-44-4, 3-Methylthiophene 622-58-2, 4-Methylphenyl isocyanate 623-50-7, Ethyl glycolate 634-97-9, Pyrrole-2-carboxylic acid 1195-45-5, 4-Fluorophenyl isocyanate 1591-99-7, 2,3-Dimethylphenyl isocyanate 2365-48-2, Methyl thioglycolate 2987-16-8, 3,3-Dimethylbutyraldehyde 4530-20-5, N-tert-Butoxycarbonylglycine 7040-43-9, 2-tert-Butylfuran 59997-51-2, 4,4-Dimethyl-3-oxopentanenitrile 149587-85-9 175137-03-8 216574-75-3 216574-76-4 216574-77-5
RL: RCT (Reactant)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT 1193-62-0P 14282-78-1P 23806-24-8P 27350-41-0P 56311-39-8P 59907-23-2P 216574-44-6P 216574-45-7P 216574-46-8P 216574-47-9P 216574-48-0P 216574-49-1P 216574-50-4P 216574-51-5P 216574-52-6P 216574-53-7P 216574-54-8P 216574-55-9P 216574-56-0P 216574-57-1P 216574-58-2P 216574-59-3P 216574-60-6P 216574-61-7P 216574-62-8P 216574-63-9P 216574-64-0P 216574-65-1P 216574-66-2P 216574-67-3P 216574-68-4P 216574-69-5P 216574-70-8P 216574-71-9P 216574-72-0P 216574-73-1P 216574-74-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(inhibition of **p38** kinase activity by aryl **ureas**)

IT 216574-78-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(inhibition of **p38** kinase activity by aryl **ureas**)

L14 ANSWER 3 OF 20 USPATFULL

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

AN 2001:155766 USPATFULL

TI 49 human secreted proteins

IN Moore, Paul A., Germantown, MD, United States
Ruben, Steven M., Oley, MD, United States
Olsen, Henrik S., Gaithersburg, MD, United States
Shi, Yanggu, Gaithersburg, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Florence, Kimberly A., Rockville, MD, United States
Soppet, Daniel R., Centreville, VA, United States
Lafleur, David W., Washington, DC, United States
Endress, Gregory A., Potomac, MD, United States
Ebner, Reinhard, Gaithersburg, MD, United States
Komatsoulis, George, Silver Spring, MD, United States
Duan, Roxanne D., Bethesda, MD, United States

PI US 2001021700 A1 20010913

AI US 2000-739254 A1 20001219 (9)

RLI Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED
Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

PRAI US 1998-97917 19980825 (60)
US 1998-98634 19980831 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 15462
SUMM . . . Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
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SUMM . . . as acquired immunodeficiency syndrome, autoimmunity, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's disease, scleroderma; infections, and other inflammatory diseases and complications.

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graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility,
lense tissue injury, demyelination, systemic lupus erythematosis, drug
induced hemolytic anemia, **rheumatoid arthritis**,
Sjogren's disease, and scleroderma. Moreover, the protein may represent
a secreted factor that influences the differentiation or behavior of
other. . .

SUMM . . . Therefore it is also useful as an agent for immunological
disorders including arthritis, asthma, immunodeficiency diseases such
as
AIDS, leukemia, **rheumatoid arthritis**, granulomatous
disease, inflammatory bowel disease, sepsis, acne, neutropenia,
neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated
cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
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lense tissue injury, demyelination, systemic lupus erythematosis, drug
induced hemolytic anemia, **rheumatoid arthritis**,
Sjogren's disease, and scleroderma. Moreover, the protein may represent
a secreted factor that influences the differentiation or behavior of
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neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated
cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
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lense tissue injury, demyelination, systemic lupus erythematosis, drug
induced hemolytic anemia, **rheumatoid arthritis**,
Sjogren's disease, and scleroderma. Moreover, the protein may represent
a secreted factor that influences the differentiation or behavior of
other. . .

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AIDS, leukemia, **rheumatoid arthritis**, granulomatous
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neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated
cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
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lense tissue injury, demyelination, systemic lupus erythematosis, drug
induced hemolytic anemia, **rheumatoid arthritis**,
Sjogren's disease, and scleroderma. Moreover, the protein may represent
a secreted factor that influences the differentiation or behavior of
other. . .

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AIDS, leukemia, **rheumatoid arthritis**, granulomatous
disease, inflammatory bowel disease, sepsis, acne, neutropenia,

neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other. . . trauma, tendonitis, chrondomalacia and inflammation). The protein is also useful in the diagnosis or treatment of various autoimmune disorders (i.e., **rheumatoid arthritis**, lupus, scleroderma, and dermatomyositis), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II,.
. .
SUMM . . . Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other. . .
SUMM . . . and/or diagnosed or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, **rheumatoid arthritis**, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's. . .
SUMM . . . degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; **rheumatoid arthritis**; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals;. . .
SUMM . . . tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, **rheumatoid arthritis**, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia,.
. .
SUMM . . . multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and **rheumatoid arthritis**) and
viral infections (such as herpes viruses, pox viruses and adenoviruses),
inflammation, graft v. host disease, acute graft rejection, and. . .

SUMM . . . multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and **rheumatoid arthritis**) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke. . .

DETD . . . be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M **urea** gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed. . .

DETD . . . of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as **rheumatoid arthritis**.

DETD . . . assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, **p38** MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any. . .

DETD . . . degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; **rheumatoid arthritis**; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals;. . .

L14 ANSWER 4 OF 20 USPATFULL

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

AN 2001:139604 USPATFULL

TI 29 human secreted proteins

IN Ruben, Steven M., Olney, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Fan, Ping, Gaithersburg, MD, United States
Kyaw, Hla, Frederick, MD, United States
Wei, Ying-Fei, Berkeley, CA, United States

PI US 2001016647 A1 20010823

AI US 2000-729835 A1 20001206 (9)

RLI Division of Ser. No. US 1999-257179, filed on 25 Feb 1999, PENDING Continuation-in-part of Ser. No. WO 1998-US17709, filed on 27 Aug 1998, UNKNOWN

PRAI US 1997-56270 19970829 (60)
US 1997-56271 19970829 (60)
US 1997-56247 19970829 (60)
US 1997-56073 19970829 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 6098

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, **rheumatoid arthritis**, inflammatory bowel disease, sepsis, acne, and psoriasis. and tissues. In addition, this gene product may have commercial utility in the. . .

SUMM . . . may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, **rheumatoid arthritis**, inflammatory bowel disease, sepsis, acne, and psoriasis. and tissues. In addition, this gene product may have commercial utility in the. . .

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SUMM . . . may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, **rheumatoid arthritis**, inflammatory bowel disease, sepsis, acne, and psoriasis. and tissues. In addition, this gene product may have commercial utility in the. . .

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gene product may have commercial utility in the. . .
SUMM . . . be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, **rheumatoid arthritis**, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's. . .
DETD . . . be successfully refolded while immobilized on the Ni--NTA column. The recommended conditions are as follows: renature using a linear 6M-1M **urea** gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed. . .
DETD . . . of NF-.kappa.B could be used to treat those diseases related to the acute or chronic activation of NF-.kappa.B, such as **rheumatoid arthritis**.
DETD . . . assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, **p38** MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any. . .

L14 ANSWER 5 OF 20 USPATFULL
AB The present invention relates to 36 novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.
AN 2001:128901 USPATFULL
TI 36 human secreted proteins
IN LaFleur, David W., Washington, DC, United States
Soppet, Daniel R., Centreville, VA, United States
Olsen, Henrik, Gaithersburg, MD, United States
Ruben, Steven M., Olney, MD, United States
Ni, Jian, Rockville, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Brewer, Laurie A., St. Paul, MN, United States
Duan, Roxanne, Bethesda, MD, United States
Ebner, Reinhard, Gaithersburg, MD, United States
PI US 2001012889 A1 20010809
AI US 2000-739907 A1 20001220 (9)
RLI Continuation of Ser. No. US 1999-348457, filed on 7 Jul 1999, ABANDONED Continuation-in-part of Ser. No. WO 1999-US108, filed on 6 Jan 1999, UNKNOWN
PRAI US 1998-70704 19980107 (60)
US 1998-70658 19980107 (60)
US 1998-70692 19980107 (60)
US 1998-70657 19980107 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 10341
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

SUMM . . . Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

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AIDS, leukemia, **rheumatoid arthritis**, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

SUMM . . . Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

SUMM . . . Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as
AIDS, leukemia, **rheumatoid arthritis**, granulomatou's

Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

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AIDS, leukemia, **rheumatoid arthritis**, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted. . .
graft-versus-host
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, **rheumatoid arthritis**, Sjogren's Disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells. . .

SUMM . . . the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chrondomalacia and inflammation, etc.), autoimmune disorders (i.e., **rheumatoid arthritis**, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, amd chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II,. . .

SUMM . . . this gene shares sequence homology with cathepsin b, a cysteine
protease which is thought to be important in demyelination, emphysema, **rheumatoid arthritis**, and neoplastic infiltration. Based on the sequence similarity, the translation product of this gene is expected to share at least. . .

SUMM . . . in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, demyelination, emphysema, **rheumatoid arthritis**, neoplastic infiltration, atherosclerosis, restenosis, thrombosis and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological. . . that the protein product of this gene is useful for the treatment and diagnosis of pathologies such as demyelination, emphysema, **rheumatoid arthritis** and neoplastic infiltration. In addition, the expression of this gene in
endothelial tissues and cells indicates that it is useful. . .

SUMM . . . it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, **rheumatoid arthritis**, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may
have commercial utility in the expansion of. . .

SUMM . . . it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, **rheumatoid arthritis**, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may
have commercial utility in the expansion of. . .

SUMM . . . be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, **rheumatoid arthritis**, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's. . .

DETD . . . be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M **urea** gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed. . .

DETD . . . of NF-.kappa.B could be used to treat those diseases related to the acute or chronic activation of NF-.kappa.B, such as **rheumatoid arthritis**.

DETD . . . assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, **p38** MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any. . .

L14 ANSWER 6 OF 20 USPATFULL

AB The present invention relates to a novel human protein called Prostate Derived Ets Factor, and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to this novel human protein.

AN 2001:123426 USPATFULL

TI PROSTATE DERIVED ETS FACTOR

IN LIBERMANN, TOWIA ARON, NEWTON, MA, United States
OETTGEN, JOERG PETER, BROOKLINE, MA, United States
KUNSCH, CHARLES A., NORCROSS, GA, United States
ENDRESS, GREGORY A., POTOMAC, MD, United States
ROSEN, CRAIG A., LAYTONSVILLE, MD, United States

PI US 2001010934 A1 20010802

AI US 1998-126945 A1 19980731 (9)

DT Utility

FS APPLICATION

LREP STERNE KESSLER GOLDSTEIN AND FOX, SUITE 600, 1100 NEW YORK AVENUE N W, WASHINGTON, DC, 200053934

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN 10 Drawing Page(s)

LN.CNT 4218

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . that can be treated or detected by PDEF include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, **rheumatoid arthritis**, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's. . .

DETD . . . be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M **urea** gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should

be performed. . .
DETD . . . of NF-.kappa.B could be used to treat those diseases related to
the acute or chronic activation of NF-.kappa.B, such as **rheumatoid arthritis.**
DETD . . . assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf,
JNK, **p38** MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any. . .

L14 ANSWER 7 OF 20 USPATFULL
AB Compounds of general formula (I) wherein: R.sup.1 is H or optionally joined with R.sup.2 to form a fused ring selected from the group consisting of five to ten membered aryl, heteroaryl or heterocyclyl rings, R.sup.2 and R.sup.3 are independently H, HET, aryl, C.sub.1-12 aliphatic, CN, NO.sub.2, halogen, R.sup.10, --OR.sup.10, --SR.sup.10, --S(O)R.sup.10, --SO.sub.2 R.sup.10, --NR.sup.10 R.sup.11, --NR.sup.11 R.sup.12, --NR.sup.12 COR.sup.11, --NR.sup.12 CO.sub.2 R.sup.11, --NR.sup.12 CONR.sup.11 R.sup.12, --NO.sup.12 SO.sub.2 R.sup.11, --NR.sup.12 C(NR .sup.12)NHR.sup.11, --COR.sup.11, --CO.sub.2 R.sup.11, --CONR.sup.12 R.sup.11, --SO.sub.2 NR.sup.12 R.sup.11, --OCONR.sup.12 R.sup.11, C(NR.sup.12)NR.sup.12 R.sup.11, R.sup.6 and R.sup.7 are independently halogen, CN, NO.sub.2, --CONR.sup.10 R.sup.11, --SO.sub.2 NR.sup.10 R.sup.11, --NR.sup.10 R.sup.11, or --OR.sup.11, where R.sup.10 and R.sup.11 are as defined below; R.sup.8 is OH, NHSO.sub.2 R.sup.12 or NHCOCF.sub.3 ; and their use in therapy, especially in the treatment of disorders mediated by cRaf1 kinase.
AN 2001:121498 USPATFULL
TI Benzylidene-1,3-dihydro-indol-2-one derivatives a receptor tyrosine kinase inhibitors, particularly of Raf kinases
IN Dickerson, Scott Howard, Chapel Hill, NC, United States
Harris, Philip Anthony, Raleigh, NC, United States
Hunter, III, Robert Neil, Raleigh, NC, United States
Jung, David Kendall, Durham, NC, United States
Lackey, Karen Elizabeth, Hillsborough, NC, United States
McNutt, Jr., Robert Walton, Durham, NC, United States
Peel, Michael Robert, Chapel Hill, NC, United States
Veal, James Marvin, Apex, NC, United States
PA Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)
PI US 6268391 B1 20010731
WO 9910325 19990304
AI US 2000-446586 20000407 (9)
WO 1998-EP4844 19980804
20000407 PCT 371 date
20000407 PCT 102(e) date
PRAI GB 1997-16557 19970806
DT Utility
FS GRANTED
EXNAM Primary Examiner: Aulakh, C. S.
LREP Lemanowicz, John L.
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3662
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK4, flt-1, Fps,

Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, **p38**, PDGFR, PIK, PKC, PYK2, ros, tie.sub.1, tie.sub.2, TRK, Yes and Zap70. In mammalian biology, such protein kinases comprise mitogen activated. . .

SUMM . . . (Tanaka et al., 1996), (5) inhibition of GSK-3 kinase in type-2 diabetes (Borthwick et al., 1995); (6) inhibition of the **p38** kinase in inflammation (Badger et al., 1996); (7) inhibition of VEGF-R 1-3 and TIE-1 and -2 kinases in angiogenesis (Shawver. . .

SUMM . . . FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK4, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, cRaf1, **p38**, PDGFR, PIK, PKC, PYK2, ros, tie.sub.1, tie.sub.2, TRK, Yes, and Zap70, said method comprising the step of administering to a. . .

SUMM . . . organ transplant rejection, healing a chronic wound, or of treating a disease state selected from the group consisting of restenosis, **rheumatoid arthritis**, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, diabetes mellitus, inflammation, and neurodegenerative disease,. . .

SUMM DMPU=1,3-dimethylpropylene **urea**

SUMM . . . 45.degree. C. Further functionalization to various heterocyclic groups may be achieved through treatment of (IIIe) with diversely substituted amidines, thioamides, **ureas** and substituted aminopyridines. For example, (IIIe) may be converted to (IIIf) by treating (IIIe) with thioacetamide in a suitable solvent. . .

L14 ANSWER 8 OF 20 USPATFULL

AB Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy.

AN 2001:97936 USPATFULL

TI Cycloalkyl substituted imidazoles

IN Adams, Jerry Leroy, Wayne, PA, United States
Boehm, Jeffrey Charles, King of Prussia, PA, United States
Garigipati, Ravi Shanker, West Warwick, RI, United States
Sorenson, Margaret, Meriden, CT, United States

PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

PI US 6251914 B1 20010626
WO 9901452 19990114

AI US 1999-445857 19991215 (9)
WO 1998-US13800 19980701
19991215 PCT 371 date
19991215 PCT 102(e) date

PRAI US 1997-51510 19970702 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Ramsuer, Robert W.

LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 3108

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . protein kinases involved were not identified. Working from a similar perspective, Han [Han, et al., Science 265, 808(1994)] identified murine **p38** as a kinase which is tyrosine phosphorylated in response to LPS. Definitive proof of the involvement

of the **p38** kinase in LPS-stimulated signal transduction pathway leading to the initiation of proinflammatory cytokine biosynthesis was provided by the independent discovery of **p38** kinase by Lee [Lee; et al., Nature, 372, 739(1994)] as the molecular target for a novel class of anti-inflammatory agents. The discovery of **p38** (termed by Lee as CSBP 1 and 2) provided a mechanism of action of a class of anti-inflammatory compounds for. . .

DRWD It is now firmly established that CSBP/**p38** is a one of several kinases involved in a stress-response signal transduction pathway which is parallel to and largely independent. . . kinase cascade (FIG. 1). Stress signals, including LPS, pro-inflammatory cytokines, oxidants, UV light and osmotic stress, activate kinases upstream from CSBP/**p38** which in turn phosphorylate CSBP/**p38** at threonine 180 and tyrosine 182 resulting in CSBP/**p38** activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/**p38** which in turn phosphorylate heat shock protein Hsp 27 (FIG. 2). It is not yet known whether MAPKAP-2, MAPKAP-3, Mnk1 or Mnk2 are involved in cytokine biosynthesis or alternatively that inhibitors of CSBP/**p38** kinase might regulate cytokine biosynthesis by blocking a yet unidentified substrate downstream from CSBP/**p38** [Cohen, P. Trends Cell Biol., 353-361(1997)].

DETD What is known, however, is that in addition to inhibiting IL-1 and TNF, CSBP/**p38** kinase inhibitors (SK&F 86002 and SB 203580) also decrease the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2. Inhibitors of CSBP/**p38** kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that CSBP/**p38** is involved not only cytokine synthesis, but also in cytokine signaling [CSBP/**P38** kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

DETD . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic .beta. cells. . .

DETD Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

DETD Inhibition of signal transduction via CSBP/**p38**, which in addition to IL-1, TNF and IL-8 described above is also required for the synthesis and/or action of several. . . and destructive activation of the immune system. This expectation is supported by the potent and diverse anti-inflammatory activities described for CSBP/**p38** kinase inhibitors [Badger, et al., J. Pharm. Exp. Thera. 279 (3): 1453-1461.(1996); Griswold, et al, Pharmacol. Comm. 7, 323-229 (1996)].

DETD . . . treatment, in this field, for compounds which are cytokine

suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting the CSBP/**p38**/RK kinase.

DETD This invention relates to a method of treating a CSBP/RK/**p38** kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a. . .

DETD This invention relates to a method of treating a CSBP/RK/**p38** kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a. . .

DETD Yet another aspect of the present invention are the use of compounds of Formula (III) for the treatment of CSBP/**p38**/RK kinase mediated diseases as described herein, which method comprises administering to a mammal in need thereof, an effective amount of. . .

DETD . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic .beta. cells and. . .

DETD Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

DETD A new member of the MAP kinase family, alternatively termed CSBP, **p38**, or RK, has been identified independently by several laboratories [See Lee et al., Nature, Vol. 300 n(72), 739-746 (1994)]. Activation. . . biosynthesis inhibitors, of the present invention, compounds of Formula (I), have been determined to be potent and selective inhibitors of CSBP/**p38**/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the. . .

DETD . . . peroxidase-conjugated goat antirabbit antibody (Pierce, Rockford, Ill.) was added, followed by a substrate for peroxidase (1 mg/ml orthophenylenediamine with 1% **urea** peroxide). TNF.alpha. levels in the plasma samples from each animal were calculated from a standard curve generated with recombinant murine. . .

DETD . . . volume. Reactions contained (in final concentration): 25 mM Hepes, pH7.5; 8 mM MgCl.sub.2 ; 0.17 mM ATP (the Km.sub.[ATP] of **p38** (see Lee et al., Nature 300, n72 pg 639-746 (December 1994)); 2.5 uCi of [g-32P]ATP; 0.2 mM sodium orthovanadate; 1 mM DTT; 0.1% BSA; 10% glycerol; 0.67 mM T669 peptide; and 24 nM of yeast-expressed, activated and purified **p38**. Reactions were initiated by the addition of [gamma-32P]Mg/ATP, and incubated for 25 min. at 37.degree. C. Inhibitors (dissolved in DMSO). . . 75 mM phosphoric acids, and incorporated 32P was quantified using beta scintillation counter. Under these conditions, the specific activity of **p38** was 400-450 pmol/pmol enzyme, and the activity was linear for up to 2 hr of incubation. The kinase activity values. . .

CLM What is claimed is:

8. A method of treating a CSBP/RK/**p38** kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of. . .

9. The method according to claim 8 wherein the CSBP/RK/**p38** kinase mediated disease is psoriatic arthritis, Reiter's syndrome, gout, gouty arthritis, traumatic arthritis, rubella arthritis and acute synovitis, **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .
15. A method of treating a CSBP/RK/**p38** kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of. . .
16. The method according to claim 15 wherein the CSBP/RK/**p38** kinase mediated disease is psoriatic arthritis, Reiter's syndrome, gout, gouty arthritis, traumatic arthritis, rubella arthritis and acute synovitis, **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, or toxic shock. . .
17. The method according to claim 16 wherein the CSBP/RK/**p38** kinase mediated disease is stroke, congestive heart failure, thrombosis, cardiac reperfusion injury, or renal reperfusion injury.

L14 ANSWER 9 OF 20 USPATFULL
AB The present invention is directed to the use of 2,4,5-trisubstituted imidazole compounds and compositions in the treatment of CNS injuries to the brain.
AN 2001:75412 USPATFULL
TI Treatment for CNS injuries
IN Feuerstein, Giora Z., Wynnewood, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6235760 B1 20010522
WO 9735855 19971002
AI US 1998-155029 19980917 (9)
WO 1997-US4702 19970324
19980917 PCT 371 date
19980917 PCT 102(e) date
PRAI US 1996-14138 19960325 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Aulakh, C. S.
LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1490
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis,

muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic .beta. cells.

SUMM Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

SUMM . . . inhibitors are those compounds of Formula (I) as noted herein. The preferred method of inhibition is the inhibition of the CSBP/**p38**/RK kinase pathway.

SUMM N-Hydroxy-N-1-[4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl]ethyl]**urea**

SUMM N-Hydroxy-N-[4-[4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]phenyl]methyl **urea**

SUMM . . . administering to said mammal an effective amount of a CSAID.TM. cytokine suppresive compound, wherein the compound is an inhibitor of CSBP/**p38**/RK kinase. Preferably, the cytokine inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

SUMM The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF, and CNSP/**p38** is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF. . .

SUMM As used herein, the term "CSBP, **p38**, or RK kinase" means a member of the MAP kinase family, which has been identified independently by several laboratories, and. . .

L14 ANSWER 10 OF 20 USPATFULL

AB This invention relates generally to N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, pharmaceutical compositions comprising the same, and methods of using the same in the treatment of inflammation and as an anticancer radiosensitizing agent.

AN 2001:52075 USPATFULL

TI N-adamant-1-yl-N1-[4-chlorobenzothiazol-2-yl] **urea** useful in the treatment of inflammation and as an anticancer radiosensitizing agent

IN Duncia, John J. V., Hockessin, DE, United States
Gardner, IV, Daniel S., Wilmington, DE, United States
Santella, III, Joseph B, Springfield, PA, United States

PA DuPont Pharmaceuticals Company, Wilmington, DE, United States (U.S. corporation)

PI US 6214851 B1 20010410

AI US 2000-527331 20000317 (9)

PRAI US 1999-125331 19990319 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Reamer, James H

LREP Wilk-Orescan, Rosemarie, Rubin, Kenneth

CLMN Number of Claims: 7

ECL Exemplary Claim: 1,6

DRWN No Drawings

LN.CNT 693

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI N-adamant-1-yl-N1-[4-chlorobenzothiazol-2-yl] **urea** useful in the treatment of inflammation and as an anticancer radiosensitizing agent

AB This invention relates generally to N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, pharmaceutical compositions comprising the same, and methods of using the same in the treatment of inflammation and as an anticancer. . .

SUMM This invention relates generally to N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, pharmaceutical compositions comprising the same, and methods of using the same in the treatment of inflammation and as an anticancer. . .

SUMM . . . differentiation and stress responses (J. Biol. Chem. (1993) 268, 14553-14556). Four parallel pathways have been identified to date: ERK1/ERK2, JNK, **p38** and ERK5. These pathways are linear kinase cascades in that MAPKKK phosphorylates and activates MAPKK that phosphorylates and activates MAPK.. . . date, there are 7 MAPKK homologs (MEK1, MEK2, MKK3, MKK4/SEK, MEK5, MKK6, and MKK7) and 4 MAPK families (ERK1/2, JNK, **p38**, and ERK5). The MAPKK family members are unique in that they are dual-specific kinases, phosphorylating MAPKs on threonine and tyrosine.. . .

SUMM . . . immune suppression would be of value. Prevention of organ transplant rejection, graft versus host disease, lupus erythematosus, multiple sclerosis, and **rheumatoid arthritis** are potential disease targets. Effects in acute and chronic inflammatory conditions are supported by the results in neutrophils and macrophage. . .

SUMM U.S. Pat. No. 5,099,021 describes a process for the preparation of unsymmetrically disubstituted **ureas**, but does not include an adamantyl moiety.

SUMM Accordingly, one object of the invention is to provide the compound N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, pharmaceutically acceptable prodrug and salt forms thereof.

SUMM . . . to provide a novel method of treating a condition or disease wherein the disease or condition is referred to as **rheumatoid arthritis**, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis. . .

SUMM Thus, in a first embodiment of the present invention the compound N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, can be made by the reactions described in Scheme 1. Reaction of the 2-amino-4-chlorobenzothiazole 1 with the carbamoyl chloride of adamantamine (2) yields **urea** 3 (for reactions of carbamoyl chlorides, see Wolf, F. J. et al., J. Am. Chem. Soc. (1954), 76, 256; Carter,. . . sequence can also be reversed so that adamantamine 5 can react with the carbamoyl chloride of 2-amino-4-chlorobenzothiazole 4 to yield **urea** 3. Carbamoyl chlorides can be synthesized by the method of Hintze, F., and Hoppe, D. (Synthesis (1992) 12, 1216-1218).

SUMM 2-Amino-4-chlorobenzothiazole 1 can also be reacted with 1-adamantylisocyanate 6 to yield **urea** 3 and the sequence can also be performed in reverse (7+5 yielding 3). Isocyanates may be synthesized by the following. . .

SUMM . . . N.; Raiford, L. C.; J. Org. Chem. (1945), 10). Diplacement of the intermediate carbamate with adamantanamine 5 yields the corresponding **urea** 3. The above sequence can be reversed so that reaction of adamantamine 5 with a chloroformate such as o-, p-nitrophenylchloroformate,. . . temperature anywhere from -78.degree. C. to room temperature, yields intermediate carbamate 8. Further reaction with 2-amino-4-chlorobenzo thiazole yields the corresponding **urea** 3.

SUMM An additional reaction sequence that leads to **urea** 3 involves the reaction of carbonyldiimidazole (CDI) (Romine, J. L.; Martin, S. W.;

Meanwell, N. A.; Epperson, J. R.; Synthesis. . . reaction may also be performed in the reversed sequence (adamantamine +CDI, followed by 2-amino-4-chlorobenzothiazole). Activation of imidazolide intermediates also facilitates **urea** formation (Bailey, R. A., et al., Tet. Lett. (1998), 39, 6267-6270).

SUMM The **urea**-forming reactions are performed in a non-hydroxylic inert solvent such as THF, toluene, DMF, methylene chloride, chloroform, carbon tetrachloride, and the. . .

DETD Preparation of N-adamant-1-yl-N'-(4-chlorobenzothiazol-2-yl)**urea**

DETD Part B. Preparation of N-adamant-1-yl-N'-(4-chlorobenzothiazol-2-yl) **urea**

DETD . . . embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, or a pharmaceutically acceptable salt form thereof.

DETD . . . of an inflammatory disease, comprising: administering to a host in need of such treatment a therapeutically effective amount of N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea**, or a pharmaceutically acceptable salt form thereof.

DETD . . . proliferative diseases by radiosensitization, comprising: administering to a host in need of such treatment a therapeutically effective amount of N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea** or a pharmaceutically acceptable salt form thereof.

DETD In another embodiment, the present invention provides N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea** or a pharmaceutically acceptable salt form thereof for the manufacture of a medicament for the treatment of an inflammatory disease.

DETD In another embodiment, the present invention provides N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea** or a pharmaceutically acceptable salt form thereof for the manufacture of a medicament for the treatment of cancer or a. . .

DETD In another embodiment, the present invention provides N-adamant-1-yl-N'-[4-chlorobenzothiazol-2-yl] **urea** or a pharmaceutically acceptable salt form thereof for use in therapy.

CLM What is claimed is:

1. A compound, N-Adamant-1-yl-N'-[4-Chlorobenzothiazol-2-yl] **Urea**.

6. A method of treating a condition or disease wherein the disease or condition is referred to as **rheumatoid arthritis**, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis. . .

L14 ANSWER 11 OF 20 USPATFULL

AB The invention provides three human cell division regulators (HCDR) and polynucleotides which identify and encode HCDR. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for preventing and treating disorders associated with expression of HCDR.

AN 2000:124797 USPATFULL

TI Cell division regulators

IN Hillman, Jennifer L., Mountain View, CA, United States
Bandman, Olga, Mountain View, CA, United States
Lal, Preeti, Sunnyvale, CA, United States

Shah, Purvi, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 6121019 20000919
AI US 1999-274570 19990323 (9)
RLI Division of Ser. No. US 1998-165234, filed on 1 Oct 1998, now patented, Pat. No. US 5928899 which is a division of Ser. No. US 1997-951148, filed on 15 Oct 1997, now patented, Pat. No. US 5871973
DT Utility
FS Granted
EXNAM Primary Examiner: Achutamurthy, Ponnathapu; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 26 Drawing Figure(s); 26 Drawing Page(s)
LN.CNT 3015
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . Cdc21p gene (Coxon, A. et al. (1992) Nucleic Acids Res. 20: 5571-5577), and a murine cell cycle-specifically modulated nuclear protein, **p38**-2G4 (Radomski, N. and Jost, E. (1995) Exp. Cell Res. 220: 434-445). **p38**-2G4 is a nuclear protein of 38 kDa and is a murine homolog of S. pombe Cdc21p gene product. **p38**-2G4 shows its highest expression between the G1 phase and the mid S phase and contains a number of putative phosphorylation. . .
DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, flugal, parasitic, protozoal, and helminthic infections. . .
DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections. . .
DETD . . . conditions that disrupt antibody/HCDR binding (eg, a buffer of pH 2-3 or a high concentration of a chaotrope, such as **urea** or thiocyanate ion), and HCDR is collected.

L14 ANSWER 12 OF 20 USPATFULL
AB Methods are provided for inhibiting the expression of cell adhesion molecules using inhibitors of signaling molecules involved in human TNF-.alpha. signaling. These inhibitors include monoclonal antibodies, peptide fragments, small molecule inhibitors, and, preferably, antisense oligonucleotides. Methods for treatment of diseases, particularly inflammatory and immune diseases, associated with overexpression of cell adhesion molecules are provided.
AN 2000:117898 USPATFULL
TI Methods of modulating tumor necrosis factor .alpha.-induced expression

of cell adhesion molecules
IN Monia, Brett P., La Costa, CA, United States
Xu, Xiaoxing S., Maddison, NJ, United States
PA Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)
PI US 6114517 20000905
AI US 1998-209668 19981210 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Epps, Janet L.
LREP Law Offices of Jane Massey Licata
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 2951
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . in immune and inflammatory responses. AP-1 is activated by various MAPKs (mitogen-activated protein kinase) including ERK (extracellular-signal-regulated kinase), JNK and **p38** MAPK (Fiers, W., et al., J. Inflam., 1996, 47, 67-75; Eder, J., TIPS, 1997, 18, 319-322). NF-kB is constitutively present. . .
SUMM . . . et al., Arch. Dermatol., 1989, 125, 1371-1376). In addition, ICAM-1 expression has been detected in the synovium of patients with **rheumatoid arthritis** (Hale, et al., Arth. Rheum., 1989, 32, 22-30), pancreatic B-cells in diabetes (Campbell, et al., Proc. Natl. Acad. Sci. U.S.A.,. . .
SUMM . . . of anti-inflammatory agents with activity towards a variety of inflammatory diseases or diseases with an inflammatory component such as asthma, **rheumatoid arthritis**, allograft rejections, inflammatory bowel disease, various dermatological conditions, and psoriasis. In addition, inhibitors of ICAM-1, VCAM-1, and ELAM-1 may also. . .
DRWD FIG. 3 is a Western blot showing the effects of c-raf antisense oligonucleotides on TNF-.alpha. mediated ERK, JNK and **p38** kinase activities. Phospho-substrate-specific antibodies were used to analyze kinase activities.
DETD . . . for diagnosing abnormal inflammatory states in tissue or other samples from patients suspected of having an inflammatory disease such as **rheumatoid arthritis**. The ability of the oligonucleotides of the present invention to inhibit inflammatory processes may be employed to diagnose such states.. . .
DETD Non-surfactants include, for example, unsaturated cyclic **ureas**, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems 1991, page 92); and non-steroidal anti-inflammatory. . .
DETD To examine the effect of the c-raf antisense oligonucleotide (ISIS 12854, SEQ ID NO. 2) on ERK, JNK, and **p38** MAPK activities stimulated by TNF-.alpha., in vitro kinase assays were performed on extracts derived from cells treated with ISIS 12854. . . concentration was measured by Bradford assay. Lysate containing equal amounts of protein were incubated with primary antibody-agarose conjugates (ERK and **p38** assay; Santa Cruz Biotechnology, Santa Cruz, Calif.), or with JNK1-specific or JNK2-specific antibodies (JNK assay; Upstate Biotechnology, Lake Placid, N.Y.),. . .
DETD . . . lysis buffer and kinase buffer, the pelleted beads were incubated with 1 .mu.g of substrate (Elk-1 for ERK, ATF-2 for **p38**, and c-Jun for JNK MAPK) and 100 .alpha.M of ATP for 20

minutes at 37.degree. C. MAPK and JNK assay. . .

DETD . . . prior to cell lysis and initiation of the kinase assays. Specific antibody-conjugated agarose beads were used to immunoprecipitate ERK and **p38** MAPK, and c-Jun-conjugated agarose beads were used to precipitate JNK. Suitable substrates and ATP were added to the immunoprecipitated kinase. . .

DETD . . . ERK activity. Surprisingly, JNK activity was also inhibited by treating cells with ISIS 12854 (SEQ ID NO. 2). Activation of **p38** MAPK was not affected by c-raf antisense treatment.

L14 ANSWER 13 OF 20 USPATFULL

AB This invention relates to the novel amino substituted pyrimidine compounds of Formulas (I), (II) and (III), and pharmaceutical compositions comprising a compound of these Formulas and a pharmaceutically acceptable diluent or carrier.

This invention also relates to a method of inhibiting CSBP kinase and cytokines mediated by this kinase, for the treatment of cytokine mediated diseases, in mammals, by administration of a compound of Formula (I), (II) or (III). ##STR1##

AN 2000:98433 USPATFULL

TI Pyrimidine compounds useful in treating cytokine mediated diseases

IN Gallagher, Timothy F., Harlesyville, PA, United States
Thompson, Susan M., Phoenixville, PA, United States

PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

PI US 6096748 20000801
WO 9733883 19970918

AI US 1998-142719 19980914 (9)
WO 1997-US4121 19970313
19980914 PCT 371 date
19980914 PCT 102(e) date

PRAI US 1996-13357 19960313 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Rao, Deepak R.

LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1729

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic .beta. cells.

SUMM Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

DETD . . . reference herein. Pyrimidine 3 can be converted to additional

compounds of Formula (I) wherein R.sub.3 is the corresponding sulphonamide, amide, **urea**, guanidine or urethane by using techniques well known to those of skill in the art of the appropriate acylating agents,. . .

DETD . . . in the art. For instance, when R.sub.3 is a dialkyl amine, R.sub.4 can be converted to the corresponding sulphonamide, amide, **urea**, guanidine or urethane by using the appropriate acylating agents such as sulfonyl chlorides, acid chlorides, isocyanates, dicyanamides and chloroformates, respectively.. . .

DETD . . . herein. Pyrimidine 5 can be converted to to additional compounds of Formula (III) wherein R.sub.4 is the corresponding sulphonamide, amide, **urea**, guanidine or urethane by using the appropriate acylating agents such as sulfonyl chlorides, isocyanates, dicyanamides and chloroformates, respectively. While it. . .

DETD . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IEL-1 activity to diabetes, pancreatic .beta. cells and. . .

DETD Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

DETD A new member of the MAP kinase family, alternatively termed CSBP, **p38**, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has. . . necrosis factor. The cytokine biosynthesis inhibitors of the present invention may be determined to be potent and selective inhibitors of CSBP/**p38**/RK kinase activity by the assay as described herein. These inhibitors are of aid in determining the signaling pathways involvement in. . .

CLM What is claimed is:

1. A method of treating a CSBP/RK/**p38** kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a. . .

7. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis or other arthritic condition.

8. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is sepsis, septic shock, endotoxic shock, gram negative sepsis, or toxic shock syndrome.

9. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is Alzheimer's disease, or cerebral malaria.

10. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, or

pulmonary sarcososis.

11. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is inflammatory bowel disease, Crohn's disease, or ulcerative colitis.

12. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

13. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is bone resorption disease, or osteoporosis.

14. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularnephritis, or diabetes.

15. The method according to claim 1 wherein the CSBP/RK/**p38** kinase mediated disease is graft vs. host reaction, allograft rejection,
multiple sclerosis, or muscle degeneration.

L14 ANSWER 14 OF 20 USPATFULL
AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I: ##STR1## wherein R.sup.1, R.sup.2, Ar.sup.1 and HetAr.sup.2 are as described in the specification.
AN 2000:88323 USPATFULL
TI Substituted pyrazoles suitable as **p38** kinase inhibitors
IN Anantanarayan, Ashok, Hainesville, IL, United States
Clare, Michael, Skokie, IL, United States
Geng, Lifeng, Skokie, IL, United States
Hanson, Gunnar J., Skokie, IL, United States
Partis, Richard A., Evanston, IL, United States
Stealey, Michael A., Libertyville, IL, United States
Weier, Richard M., Lake Bluff, IL, United States
PA G. D. Searle & Co., Chicago, IL, United States (U.S. corporation)
PI US 6087496 20000711
AI US 1999-283718 19990401 (9)
RLI Continuation of Ser. No. US 1998-83923, filed on 22 May 1998, now patented, Pat. No. US 5932576
PRAI US 1997-47535 19970522 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Higel, Floyd D.
LREP Bulock, Joseph W., Scrivner, Alan L.
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1992
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Substituted pyrazoles suitable as **p38** kinase inhibitors
AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I: ##STR1## wherein R.sup.1, R.sup.2, Ar.sup.1 and HetAr.sup.2 are. . .
SUMM This invention relates to a novel group of pyrazole compounds, compositions and methods for treating **p38** kinase mediated disorders.

SUMM . . . activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. The **p38** MAP kinase group is a MAP family of various isoforms, including **p38**.alpha., **p38**.beta. and **p38**.gamma., and is responsible for phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other kinases (e.g. MAPKAP-2 and MAPKAP-3). The **p38** isoforms are activated by bacterial lipopolysaccharide, physical and chemical stress and by pro-inflammatory cytokines, including tumor necrosis factor (TNF-.alpha.) and interleukin-1 (IL-1). The products of the **p38** phosphorylation mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2.

SUMM . . . implicated in mediating a number of diseases. Recent studies indicate that TNF has a causative role in the pathogenesis of **rheumatoid arthritis**. Additional studies demonstrate that inhibition of TNF has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis. . .

SUMM . . . activated monocytes and macrophages and is involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including **rheumatoid arthritis**, fever and reduction of bone resorption.

SUMM . . . inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition of the **p38** kinase is of benefit in controlling, reducing and alleviating many of these disease states.

SUMM The invention's pyrazolyl compounds are found to show usefulness as **p38** kinase inhibitors.

SUMM A class of substituted pyrazolyl compounds useful in treating **p38** mediated disorders is defined by Formula I: ##STR2## wherein

SUMM . . . or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated TNF or **p38** kinase production by such mammal. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering. . .

SUMM . . . for the treatment of fever. Compounds of the invention would be useful to treat arthritis, including but not limited to, **rheumatoid arthritis**, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Such compounds would. . .

SUMM As used herein, the term "**p38** mediated disorder" refers to any and all disorders and disease states in which **p38** plays a role, either by control of **p38** itself, or by **p38** causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in. . . which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to **p38**, would therefore be considered a disorder mediated by **p38**.

SUMM [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**;

SUMM The present invention comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation, and/or arthritis, comprising a therapeutically-effective amount of a compound of Formula I, or a therapeutically-acceptable salt. . .

SUMM The present invention also comprises a therapeutic method of treating a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such. . .

DETD [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**

DETD . . . and the residue was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and methanol. The purified [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea** thus obtained had m.p. 224-225.degree. C.

DETD **p38** Kinase Assay

DETD . . . reagents were all purchased from Life-Technologies, Gaithersburg, Mass. The reaction was incubated at 42.degree. C. for 1 hour. Amplification of **p38** cDNA was performed by aliquoting 5 .mu.l of the reverse transcriptase reaction into a 100 .mu.l PCR reaction containing the. . .

DETD Purification of **P38** Kinase-.alpha.

DETD . . . centrifugation (600.times.g, 5 min) and washed with 2.times.150 ml PBS/1% Triton X-100, followed by 4.times.40 ml PBS. To cleave the **p38** kinase from the GST-**p38** fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity >7500. . . removed by centrifugation (600.times.g, 5 min) and washed 2.times.6 ml with PBS. The PBS wash fractions and digest supernatant containing **p38** kinase protein were pooled and adjusted to 0.3 mM PMSF.

DETD The thrombin-cleaved **p38** kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH. . . Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The **p38** kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron. . .

DETD The concentrated Mono Q- **p38** kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50. . . column with Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm. Fractions containing **p38** kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80.degree. C. Typical purified protein yields from 5 L E. coli shake flasks fermentations were 35 mg **p38** kinase.

DETD The ability of compounds to inhibit human **p38** kinase alpha was evaluated using two in vitro assay methods. In the first method, activated human **p38** kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma .sup.32. . . was biotinylated prior to the assay and provides a means of capturing the substrate which is phosphorylated during the assay. **p38** Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 .mu.M to. . .

DETD . . . Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 .mu.M unlabeled ATP. Activation of **p38** was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 .mu.g per 50 .mu.l reaction volume, with a final concentration of 1.5 .mu.M. Activated human **p38** kinase alpha was used at 1 .mu.g per 50 .mu.l reaction volume representing a final concentration of 0.3 .mu.M. Gamma. . .

DETD A second assay format was also employed that is based on **p38** kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence of .sup.33 P-ATP.. . . (200 .mu.M), and 0.05 uCi gamma .sup.33 P-ATP. Reactions were initiated by addition of 0.09 .mu.g of activated, purified human GST-**p38** kinase alpha. Activation was carried out using GST-MKK6 (5:1,**p38** :MKK6) for one hour at 30.degree. C. in the presence of 50 .mu.M ATP.

Following incubation for 60 minutes at room. . .

DETD Results obtained using the above-described assays are set forth in Table

I below. **p38** assay and U937 cell assay results are expressed as IC.sub.50 (.mu.m). Mouse-LPS assay results are expressed as percent inhibition.

DETD TABLE I

Example	**P38**.alpha..sup.1 (.mu.M)	**p38**.alpha..sup.2 (.mu.M)	U937 (6 h @ mLPS (30 mpk)
1	30.00	13.35	10.00
2	6.21	10.61	
3	2.55	>10.00	
4.	.	.	0.4 1.5987 76
11	0.695	10	40
12	0.941	10	-5
13	0.86	>10	22
15	5.9	0.75	32

.sup.1 **p38**.alpha. in vitro results based on PHASI assay procedure

.sup.2 **p38**.alpha. in vitro results based on EGFRP assay procedure

CLM What is claimed is:

. . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of: 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-(4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

34. A method of treating a **p38** kinase mediated disorder, said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of. . .

. . . mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .

. . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-

pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol -3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

42. The method of claim 34 wherein the disorder is a **p38** .alpha. kinase mediated disorder.

43. The method of claim 34 wherein the **P38** kinase mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .

44. The method of claim 34 wherein the **p38** kinase mediated disorder is inflammation.

45. The method of claim 34 wherein the **p38** kinase mediated disorder is arthritis.

46. The method of claim 34 wherein the **p38** kinase mediated disorder is asthma.

. . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

L14 ANSWER 15 OF 20 USPATFULL

AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I ##STR1## wherein Q, R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as described in the specification.

AN 2000:88210 USPATFULL

TI Pyrazole derivatives as **p38** kinase inhibitors

IN Hanson, Gunnar J., Skokie, IL, United States
Liao, Shuyuan, Glenn Ellyn, IL, United States

PA G. D. Searle & Company, Skokie, IL, United States (U.S. corporation)

PI US 6087381 20000711

AI US 1998-83724 19980522 (9)

PRAI US 1997-47569 19970522 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Stockton, Laura L.

LREP Senniger, Powers, Leavitt & Roedel

CLMN Number of Claims: 41

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1940

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Pyrazole derivatives as **p38** kinase inhibitors

AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I ##STR1## wherein Q, R.sup.1, R.sup.2, R.sup.3 and R.sup.4. . .

SUMM This invention relates to a novel group of pyrazole compounds, compositions and methods for treating **p38** kinase mediated disorders.

SUMM . . . activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. The **p38** MAP kinase group is a MAP family of various isoforms, including **p38**.alpha., **p38**.beta. and **p38**.gamma., and is responsible for phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other kinases (e.g. MAPKAP-2 and MAPKAP-3). The **p38** isoforms are activated by bacterial lipopolysaccharide, physical and chemical stress and by pro-inflammatory cytokines, including tumor necrosis factor (TNF-.alpha.) and interleukin-1 (IL-1). The products of the **p38** phosphorylation mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2.

SUMM . . . implicated in mediating a number of diseases. Recent studies indicate that TNF has a causative role in the pathogenesis of **rheumatoid arthritis**. Additional studies demonstrate that inhibition of TNF has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis. . .

SUMM . . . activated monocytes and macrophages and is involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including **rheumatoid arthritis**, fever and reduction of bone resorption.

SUMM . . . inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition of the **p38** kinase is of benefit in controlling, reducing and alleviating many of these disease states.

SUMM The invention's pyrazolyl compounds are found to show usefulness as **p38** kinase inhibitors.

SUMM A class of substituted pyrazolyl compounds useful in treating **p38** mediated disorders is defined by Formula I: ##STR2## wherein R.sup.1 is selected from hydrido, alkyl, cycloalkyl, alkenyl,

cycloalkenyl, alkynyl, aryl,. . .

SUMM . . . or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated TNF or **p38** kinase production by such mammal. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering. . .

SUMM . . . for the treatment of fever. Compounds of the invention would be useful to treat arthritis, including but not limited to, **rheumatoid arthritis**, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Such compounds would. . .

SUMM As used herein, the term "**p38** mediated disorder" refers to any and all disorders and disease states in which **p38** plays a role, either by control of **p38** itself, or by **p38** causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in. . . which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to **p38**, would therefore be considered a disorder mediated by **p38**.

SUMM The present invention comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation and/or arthritis, comprising a therapeutically-effective amount of a compound of Formula I-VIII, or a therapeutically-acceptable salt. . .

SUMM The present invention also comprises a therapeutic method of treating a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such. . .

SUMM General Synthetic Scheme IX shows the preparation of a subset of the pyrazoles of Formula I where Q is a **urea** bridging radical. Isocyanate 40 (prepared as set forth in Scheme V) is reacted with optionally substituted aniline 41 to give **urea** 42. ##STR30##

DETD **p38** Kinase Assay

DETD . . . reagents were all purchased from Life-Technologies, Gaithersburg, Mass. The reaction was incubated at 42.degree. C. for 1 hour. Amplification of **p38** cDNA was performed by aliquoting 5 .mu.l of the reverse transcriptase reaction into a 100 .mu.l PCR reaction containing the. . .

DETD Purification of **p38** Kinase-.alpha.:

DETD . . . centrifugation (600.times.g, 5 min) and washed with 2.times.150 ml PBS/1% Triton X-100, followed by 4.times.40 ml PBS. To cleave the **p38** kinase from the GST-**p38** fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity>7500 units/mg).

. removed by centrifugation (600.times.g, 5 min) and washed 2.times.6 ml with PBS. The PBS wash fractions and digest supernatant containing **p38** kinase protein were pooled and adjusted to 0.3 mM PMSF.

DETD The thrombin-cleaved **p38** kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH. . . Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The **p38** kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron. . .

DETD The concentrated Mono Q- **p38** kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60

Sephacryl S100 column equilibrated with Buffer B (50. . . column with
Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm. Fractions containing **p38** kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80.degree. C. Typical purified protein yields from 5 L E. coli shake flasks fermentations were 35 mg **p38** kinase.

DETD The ability of compounds to inhibit human **p38** kinase alpha was evaluated using two in vitro assay methods. In the first method, activated human **p38** kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma .sup.32. . . was biotinylated prior to the assay and provides a means of capturing the substrate which
is phosphorylated during the assay. **p38** Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 .mu.M to. . .

DETD . . . Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 .mu.M unlabeled ATP. Activation of **p38** was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 .mu.g per 50 .mu.l reaction volume, with a final concentration of 1.5 .mu.M. Activated human **p38** kinase alpha was used at 1 .mu.g per 50 .mu.l reaction volume representing a final concentration of 0.3 .mu.M. Gamma. . .

DETD A second assay format was also employed that is based on **p38** kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence of .sup.33 P-ATP.. . . (200 .mu.M), and 0.05 uCi gamma .sup.33 P-ATP. Reactions were initiated by addition of 0.09 .mu.g of activated, purified human GST-**p38** kinase alpha. Activation was carried out using GST-MKK6 (5:1,**p38** :MKK6) for one hour at 30.degree. C. in the presence of 50 .mu.M ATP. Following incubation for 60 minutes at room. . .

DETD TABLE I

Example	**p38** kinase.sup.1 IC50 .mu.M	**p38** kinase.sup.2 IC50 .mu.M
1	8.7	0.66
2	1.0	2.8

.sup.1 **p38**.alpha. in vitro assay results based on PHASI assay procedure

.sup.2 **p38**.alpha. in vitro assay results based on EGFRP assay procedure

CLM What is claimed is:

17. A method of treating a **p38** kinase mediated disorder, said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of. . .

20. The method of claim 16 wherein the **p38** TNF mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .

24. The method of claim 17 wherein the disorder is a **p38** .alpha. kinase mediated disorder.

25. The method of claim 17 wherein the **p38** kinase mediated disorder is selected from the group of diseases consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .
26. The method of claim 17 wherein the **p38** kinase mediated disorder is inflammation.

27. The method of claim 17 wherein the **p38** kinase mediated disorder is arthritis.

28. The method of claim 17 wherein the **p38** kinase mediated disorder is asthma.

30. A method of treating a **p38** kinase mediated disorder said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of. . .
33. The method of claim 29 wherein the **p38** TNF mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .
37. The method of claim 30 wherein the disorder is a **p38** .alpha. kinase mediated disorder.

38. The method of claim 30 wherein the **p38** kinase mediated disorder is selected from the group of diseases consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritic, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease stato, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .
39. The method of claim 30 wherein the **p38** kinase mediated disorder is inflammation.

40. The method of claim 30 wherein the **p38** kinase mediated disorder is arthritis.

41. The method of claim 30 wherein the **p38** kinase mediated disorder is asthma.

L14 ANSWER 16 OF 20 USPATFULL
AB Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy as cytokine inhibitors.
AN 2000:41053 USPATFULL
TI Substituted imidazole compounds
IN Adams, Jerry L., Wayne, PA, United States
Boehm, Jeffrey C., King of Prussia, PA, United States
Gallagher, Timothy Francis, Harleysville, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6046208 20000404
AI US 1998-109024 19980701 (9)
RLI Continuation-in-part of Ser. No. US 1998-62542, filed on 17 Apr 1998, now patented, Pat. No. US 5864036 which is a division of Ser. No. US

1997-780954, filed on 10 Jan 1997, now patented, Pat. No. US 5756499
PRAI US 1997-51592 19970702 (60)
US 1996-9907 19960111 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Ramsuer, Robert W.
LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 3504
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . protein kinases involved were not identified. Working from a similar perspective, Han [Han, et al., Science 265, 808(1994)] identified murine **p38** as a kinase which is tyrosine phosphorylated in response to LPS. Definitive proof of the involvement of the **p38** kinase in LPS-stimulated signal transduction pathway leading to the initiation of proinflammatory cytokine biosynthesis was provided by the independent discovery of **p38** kinase by Lee [Lee; et al., Nature, 372, 739(1994)] as the molecular target for a novel class of anti-inflammatory agents. The discovery of **p38** (termed by Lee as CSBP 1 and 2) provided a mechanism of action of a class of anti-inflammatory compounds for. . .
SUMM It is now firmly established that CSBP/**p38** is a one of several kinases involved in a stress-response signal transduction pathway which is parallel to and largely independent. . . kinase cascade (FIG. 1). Stress signals, including LPS, pro-inflammatory cytokines, oxidants, UV light and osmotic stress, activate kinases upstream from CSBP/**p38** which in turn phosphorylate CSBP/**p38** at threonine 180 and tyrosine 182 resulting in CSBP/**p38** activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/**p38** which in turn phosphorylate heat shock protein Hsp 27 (FIG. 2). It is not yet known whether MAPKAP-2, MAPKAP-3, Mnk1 or Mnk2 are involved in cytokine biosynthesis or alternatively that inhibitors of CSBP/**p38** kinase might regulate cytokine biosynthesis by blocking a yet unidentified substrate downstream from CSBP/**p38** [Cohen, P. Trends Cell Biol., 353-361(1997)].
SUMM What is known, however, is that in addition to inhibiting IL-1 and TNF, CSBP/**p38** kinase inhibitors (SK&F 86002 and SB 203580) also decrease the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2. Inhibitors of CSBP/**p38** kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that CSBP/**p38** is involved not only cytokine synthesis, but also in cytokine signaling [CSBP/**P38** kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].
SUMM . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1

activity to diabetes and pancreatic .beta. cells. . .
SUMM Excessive or unregulated TNF production has been implicated in mediating
or exacerbating a number of disease including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .
SUMM Inhibition of signal transduction via CSBP/**p38**, which in addition to IL-1, TNF and IL-8 described above is also required for the synthesis and/or action of several. . . and destructive activation of
the immune system. This expectation is supported by the potent and diverse anti-inflammatory activities described for CSBP/**p38** kinase inhibitors [Badger, et al., J. Pharm. Exp. Thera. 279 (3): 1453-1461.(1996); Griswold, et al, Pharmacol. Comm. 7, 323-229 (1996)].
SUMM . . . treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of
inhibiting the CSBP/**p38**/RK kinase.
DRWD FIG. 2 demonstrates the **p38** kinase pathway.
DETD This invention relates to a method of treating a CSBP/RK/**p38** kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a. . .
DETD . . . many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include **rheumatoid arthritis**, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by
endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic .beta. cells and. . .
DETD Excessive or unregulated TNF production has been implicated in mediating
or exacerbating a number of diseases including **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .
DETD A new member of the MAP kinase family, alternatively termed CSBP, **p38**, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has. . . biosynthesis inhibitors, of the present invention, compounds of Formula (I) have been determined to be potent and selective inhibitors of CSBP/**p38**/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the. . .
DETD . . . peroxidase-conjugated goat antirabbit antibody (Pierce, Rockford, Ill.) was added, followed by a substrate for peroxidase (1 mg/ml orthophenylenediamine with 1% **urea** peroxide). TNF.alpha. levels in the plasma samples from each animal were calculated from a standard curve generated with recombinant murine. . .
DETD . . . Reactions contained (in final concentration): 25 mM Hepes, pH 7.5; 8 mM MgCl.sub.2 ; 0.17 mM ATP (the Km.sub.[ATP] of **p38** (see Lee et al., Nature 300, n72 pg 639-746 (December 1994)); 2.5 uCi of
[g-32P]ATP; 0.2 mM sodium orthovanadate; 1 mM DTT; 0.1% BSA; 10% glycerol; 0.67 mM T669 peptide; and 2-4 nM of yeast-expressed, activated

and purified **p38**. Reactions were initiated by the addition of [gamma-32P]Mg/ATP, and incubated for 25 min at 37.degree. C. Inhibitors dissolved in DMSO). . . 75 mM phosphoric acids, and incorporated 32P was quantified using beta scintillation counter. Under these conditions, the specific activity of **p38** was 400-450 pmol/pmol enzyme, and the activity was linear for up to 2 hr of incubation. The kinase activity values. . .

CLM What is claimed is: 3. A method of treating a CSBP/RK/**p38** kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of. . . 4. The method according to claim 3 wherein the CSBP/RK/**p38** kinase mediated disease is psoriatic arthritis, Reiter's syndrome, **rheumatoid arthritis**, gout, traumatic arthritis, rubella arthritis and acute synovitis, **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,. . .

L14 ANSWER 17 OF 20 USPATFULL

AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I ##STR1##

AN 1999:89152 USPATFULL

TI 3(5)-heteroaryl substituted pyrazoles as **p38** kinase inhibitors

IN Anantanarayan, Ashok, Hainesville, IL, United States
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Partis, Richard A., Evanston, IL, United States
Stealey, Michael A., Libertyville, IL, United States
Weier, Richard M., Lake Bluff, IL, United States

PA G. D. Searle & Company, Chicago, IL, United States (U.S. corporation)

PI US 5932576 19990803

AI US 1998-83923 19980522 (9)

PRAI US 1997-47535 19970522 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Higel, Floyd D.

LREP Bulock, Joseph W., Scrivner, Alan L.

CLMN Number of Claims: 50

ECL Exemplary Claim: 1,34

DRWN No Drawings

LN.CNT 2075

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI 3(5)-heteroaryl substituted pyrazoles as **p38** kinase inhibitors

AB A class of pyrazole derivatives is described for use in treating **p38** kinase mediated disorders. Compounds of particular interest are defined by Formula I ##STR1##

SUMM This invention relates to a novel group of pyrazole compounds, compositions and methods for treating **p38** kinase mediated disorders.

SUMM . . . activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. The **p38** MAP kinase group is a MAP family of various isoforms, including **p38**.alpha., p39.beta. and **p38** .gamma., and is responsible for phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other

kinases (e.g. MAPKAP-2 and MAPKAP-3). The **p38** isoforms are activated by bacterial lipopolysaccharide, physical and chemical stress and by pro-inflammatory cytokines, including tumor necrosis factor (TNF-.alpha.) and interleukin-1 (IL-1). The products of the **p38** phosphorylation mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2.

SUMM . . . implicated in mediating a number of diseases. Recent studies indicate that TNF has a causative role in the pathogenesis of **rheumatoid arthritis**. Additional studies demonstrate that inhibition of TNF has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis. . .

SUMM . . . activated monocytes and macrophages and is involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including **rheumatoid arthritis**, fever and reduction of bone resorption.

SUMM . . . inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition of the **p38** kinase is of benefit in controlling, reducing and alleviating many of these disease states.

SUMM The invention's pyrazolyl compounds are found to show usefulness as **p38** kinase inhibitors.

SUMM A class of substituted pyrazolyl compounds useful in treating **p38** mediated disorders is defined by Formula I: ##STR2## wherein

SUMM . . . or disease state in a human, or other mammal, which is excacerbated or caused by excessive or unregulated TNF or **p38** kinase production by such mammal. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering. . .

SUMM . . . for the treatment of fever. Compounds of the invention would be useful to treat arthritis, including but not limited to, **rheumatoid arthritis**, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Such compounds would. . .

SUMM As used herein, the term "**p38** mediated disorder" refers to any and all disorders and disease states in which **p38** plays a role, either by control of **p38** itself, or by **p38** causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in. . . which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to **p38**, would therefore be considered a disorder mediated by **p38**.

SUMM [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**;

SUMM The present invention comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation, and/or arthritis, comprising a therapeutically-effective amount of a compound of Formula I, or a therapeutically-acceptable salt. . .

SUMM The present invention also comprises a therapeutic method of treating a TNF mediated disorder, a **p38** kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such. . .

DETD [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**

DETD . . . and the residue was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and methanol. The purified [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea** thus obtained had m.p. 224-225.degree. C.

DETD **p38** Kinase Assay

DETD . . . reagents were all purchased from Life-Technologies,

Gaithersburg, Mass. The reaction was incubated at 42.degree. C. for 1 hour. Amplification of **p38** cDNA was performed by aliquoting 5 .mu.l of the reverse transcriptase reaction into a 100 .mu.l PCR reaction containing the. . .

DETD Purification of **p38** Kinase-.alpha.:

DETD . . . centrifugation (600.times.g, 5 min) and washed with 2.times.150 ml PBS/1% Triton X-100, followed by 4.times.40 ml PBS. To cleave the **p38** kinase from the GST-**p38** fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity>7500 units/mg). .

. removed by centrifugation (600.times.g, 5 min) and washed 2.times.6 ml with PBS. The PBS wash fractions and digest supernatant containing **p38** kinase protein were pooled and adjusted to 0.3 mM PMSF.

DETD The thrombin-cleaved **p38** kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH. . . Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The **p38** kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron. . .

DETD The concentrated Mono Q- **p38** kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50. . . column with Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm. Fractions containing **p38** kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80.degree. C. Typical purified protein yields from 5 L E. coli shake flasks fermentations were 35 mg **p38** kinase.

DETD The ability of compounds to inhibit human **p38** kinase alpha was evaluated using two in vitro assay methods. In the first method, activated human **p38** kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma .sup.32. . . was biotinylated prior to the assay and provides a means of capturing the substrate which is phosphorylated during the assay. **p38** Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 .mu.M to. . .

DETD . . . Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 .mu.M unlabeled ATP. Activation of **p38** was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 .mu.g per 50 .mu.l reaction volume, with a final concentration of 1.5 .mu.M. Activated human **p38** kinase alpha was used at 1 .mu.g per 50 .mu.l reaction volume representing a final concentration of 0.3 .mu.M. Gamma. . .

DETD A second assay format was also employed that is based on **p38** kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence of .sup.33 P-ATP.. . . (200 .mu.M), and 0.05 uCi gamma .sup.33 P-ATP. Reactions were initiated by addition of 0.09 .mu.g of activated, purified human GST-**p38** kinase alpha. Activation was carried out using GST-MKK6 (5:1,**p38** :MKK6) for one hour at 30.degree. C. in the presence of 50 .mu.M ATP. Following incubation for 60 minutes at room. . .

DETD Results obtained using the above-described assays are set forth in Table I below. **p38** assay and U937 cell assay results are expressed as IC.sub.50 (.mu.m) . Mouse-LPS assay results are expressed as percent

inhibition.

DETD TABLE I

Example	**P38**.alpha..sup.1 (.mu.M)	**p38**.alpha..sup.2 (.mu.M)	U937 (.mu.M)	mLPS (6 h @ 30 mpk)
1	30.00	13.35	10.00	
2		6.21	10.61	
3		2.55	>10.00	
4		0.23	4.70	54
5	1.98. . .	3.46	0.6474	42
10	7.23	0.4	1.5987	76
11	0.695	10	40	
12	0.941	10	-5	
13	0.86	>10	22	
15	5.9	0.75	32	

.sup.1 **p38**.alpha. in vitro results based on PHASI assay procedure

.sup.2 **p38**.alpha. in vitro results based on EGFRP assay procedure

CLM What is claimed is:

. . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

34. A method of treating a **p38** kinase mediated disorder, said method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of. . . . . mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . . . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-

pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

42. The method of claim 34 wherein the disorder is a **p38** .alpha. kinase mediated disorder.

43. The method of claim 34 wherein the **P38** kinase mediated disorder is selected from the group of disorders consisting of bone resorption, graft vs. host reaction, atherosclerosis, arthritis, osteoarthritis, **rheumatoid arthritis**, gout, psoriasis, topical inflammatory disease state, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, cardiac reperfusion injury, renal reperfusion. . .

44. The method of claim 34 wherein the **p38** kinase mediated disorder is inflammation.

45. The method of claim 34 wherein the **p38** kinase mediated disorder is arthritis.

46. The method of claim 34 wherein the **p38** kinase mediated disorder is asthma.

. . . selected from the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of 4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine; 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine; N-[4(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]methanesulfonamide; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]**urea**; [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]sulfamide; 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine; N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea; 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine; 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine; 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol; 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine; 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine; 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine; 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]piperidine.

L14 ANSWER 18 OF 20 USPATFULL
AB The invention provides three human cell division regulators (HCDR) and polynucleotides which identify and encode HCDR. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for preventing and treating disorders associated with expression of HCDR.
AN 1999:85250 USPATFULL
TI Cell division regulators
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Shah, Purvi, Sunnyvale, CA, United States
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PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5928899 19990727
AI US 1998-165234 19981001 (9)
RLI Division of Ser. No. US 1997-951148, filed on 15 Oct 1997
DT Utility
FS Granted
EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 26 Drawing Figure(s); 26 Drawing Page(s)
LN.CNT 2866
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . pombe Cdc2lp gene (Coxon, A. et al. (1992) Nucleic Acids Res. 20:5571-5577), and a murine cell cycle-specifically modulated nuclear protein, **p38**-2G4 (Radomski, N. and Jost, E. (1995) Exp. Cell Res. 220:434-445). **p38**-2G4 is a nuclear protein of 38 kDa and is a murine homolog of S. pombe Cdc2lp gene product. **p38**-2G4 shows its highest expression between the G1 phase and the mid S phase and contains a number of putative phosphorylation. . .
DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections. . .
DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections. . .
DETD . . . conditions that disrupt antibody/HCDR binding (eg, a buffer of pH 2-3 or a high concentration of a chaotrope, such as **urea** or thiocyanate ion), and HCDR is collected.

L14 ANSWER 19 OF 20 USPATFULL
AB The invention provides three human cell division regulators (HCDR) and polynucleotides which identify and encode HCDR. The invention also

provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for preventing and treating disorders associated with expression of HCDR.

AN 1999:21954 USPATFULL
TI Cell division regulators
IN Hillman, Jennifer L., Mountain View, CA, United States
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Lal, Preeti, Sunnyvale, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5871973 19990216
AI US 1997-951148 19971015 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Hendricks, Keith D.; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 26 Drawing Figure(s); 26 Drawing Page(s)
LN.CNT 2769
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Cdc21p gene (Coxon, A. et al. (1992) Nucleic Acids Res. 20: 5571-5577), and a murine cell cycle-specifically modulated nuclear protein, **p38**-2G4 (Radomski, N. and Jost, E. (1995) Exp. Cell Res. 220: 434-445). **p38**-2G4 is a nuclear protein of 38 kDa and is a murine homolog of S. pombe Cdc21p gene product. **p38**-2G4 shows its highest expression between the G1 phase and the mid S phase and contains a number of putative phosphorylation. . .

DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections. . .

DETD . . . Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, **rheumatoid arthritis**, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal, and helminthic infections. . .

DETD . . . conditions that disrupt antibody/HCDR binding (eg, a buffer of pH 2-3 or a high concentration of a chaotrope, such as **urea** or thiocyanate ion), and HCDR is collected.

L14 ANSWER 20 OF 20 USPATFULL

AB The present invention provides polynucleotides (kin) which identify and encode novel protein kinases (KIN) expressed in various human cells and tissues. The present invention also provides for antisense sequences and oligonucleotides designed from the nucleotide sequences or their complements. The invention further provides genetically engineered

expression vectors and host cells for the production of purified KIN peptides, antibodies capable of binding KIN, and inhibitors specifically bind KIN. The invention specifically provides for diagnostic kits and assays which identify a disorder or disease with altered kinase expression and allow monitoring of patients during drug therapy. These assays utilize oligonucleotides or antibodies produced using the kin polynucleotides.

AN 1998:122235 USPATFULL
TI Human kinase homologs
IN Au-Young, Janice, Berkeley, CA, United States
Bandman, Olga, Mountain View, CA, United States
Hawkins, Phillip R., Mountain View, CA, United States
Wilde, Craig G., Sunnyvale, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5817479 19981006
AI US 1996-700575 19960807 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Eisenschenk, Frank C.; Assistant Examiner: Nolan, Patrick J.
LREP Billings, Lucy J., Mohan-Peterson, SheelaIncyte Pharmaceuticals, Inc.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2025
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . tripeptide motif. They are extracellular signal-regulated protein kinases (ERK) characterized by Thr-Glu-Tyr; c-Jun amino-terminal kinases (JNK) characterized by Thr-Pro-Tyr; and **p38** kinase characterized by Thr-Gly-Tyr. Each subgroup is activated by dual phosphorylation of threonine and tyrosine residues by MAP kinase kinases. . .
SUMM **p38** is a 41 kD protein containing 360-amino acids. Its dual phosphorylation is activated by the MKK3 and MKK4, heat shock,. . .
SUMM . . . 42-/40-kD isoforms of MAP kinases. Although they bind LPS, these MAP kinase isoforms do not appear to belong to the **p38** subgroup.
DETD Rheumatoid synovial tissue was obtained from the hip joint removed from a 68 year old female with erosive, nodular **rheumatoid arthritis**. The tissue was frozen, ground to powder in a mortar and pestle, and lysed immediately in buffer containing guanidinium isothiocyanate.. . .
DETD . . . conditions that disrupt antibody/KIN binding (eg, a buffer of pH 2-3 or a high concentration of a chaotrope such as **urea** or thiocyanate ion), and KIN is collected.

=>

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:12:05 ON 08 NOV 2001
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FILE COVERS 1947 - 8 Nov 2001  VOL 135 ISS 20
FILE LAST UPDATED: 7 Nov 2001  (20011107/ED)

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in CA from 1947 to the present.  On April 22, 2001, bibliographic
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published in CA from 1947 to 1966.

=>

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=> d stat que l8

L1                STR
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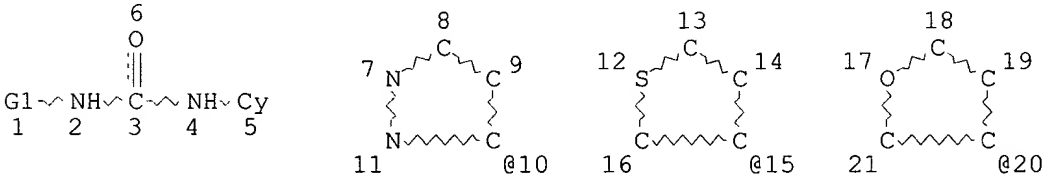


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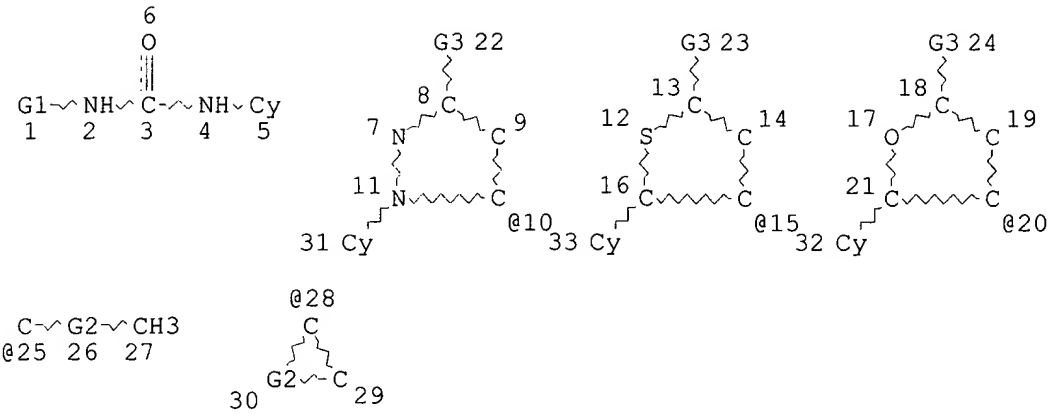

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L8 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:825371 HCAPLUS
DOCUMENT NUMBER: 134:131489
TITLE: A convenient synthesis of pyrazolo[3,4-d]pyrimidine-4,6-dione and pyrazolo[4,3-d]pyrimidine-5,7-dione derivatives
AUTHOR(S): Haddad, M. El; Soukri, M.; Lazar, S.; Bennamara, A.; Guillaumet, G.; Akssira, M.
CORPORATE SOURCE: Laboratoire de Chimie Bioorganique et Analytique, FST - Universite Hassan II - Mohammedia, Mohammedia, Morocco
SOURCE: J. Heterocycl. Chem. (2000), 37(5), 1247-1252
CODEN: JHTCAD; ISSN: 0022-152X
PUBLISHER: HeteroCorporation
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:131489
AB Pyrazolo[3,4-d]pyrimidine-4,6-diones and pyrazolo[4,3-d]pyrimidine-5,7-diones were synthesized by Curtius rearrangement of 3,4-pyrazoledicarboxylic acid monoesters followed by heterocyclization via urea derivs. under alk. conditions.
IT **321850-61-7P 321850-62-8P 321850-63-9P 321850-64-0P 321850-66-2P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of pyrazolopyrimidinediones)
IT **321850-65-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of pyrazolopyrimidinediones)
REFERENCE COUNT: 28
REFERENCE(S): (1) Ahn, H; J Med Chem 1997, V40, P2196 HCAPLUS
(4) Anderson, J; J Heterocyclic Chem 1986, V23, P1869 HCAPLUS
(5) Anderson, J; J Heterocyclic Chem 1990, V27, P439 HCAPLUS
(6) Bhat, G; J Med Chem 1981, V24, P1165 HCAPLUS
(7) Bontems, R; J Med Chem 1990, V33, P2174 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L8 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:513688 HCAPLUS
DOCUMENT NUMBER: 133:120325
TITLE: Preparation of aromatic heterocyclic ureas as antiinflammatory agents
INVENTOR(S): Cirillo, Pier F.; Gilmore, Thomas A.; Hickey, Eugene R.; Regan, John R.; Zhang, Lin-Hua
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043384	A1	20000727	WO 1999-US29165	19991209
W: AE, AU, BG, BR, BY, CA, CN, CZ, EE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, VN, YU, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1147104	A1	20011024	EP 1999-960668	19991209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001003559	A	20010718	NO 2001-3559	20010718

PRIORITY APPLN. INFO.: US 1999-116400 P 19990119
WO 1999-US29165 W 19991209
OTHER SOURCE(S): MARPAT 133:120325
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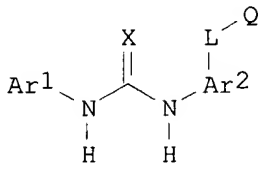

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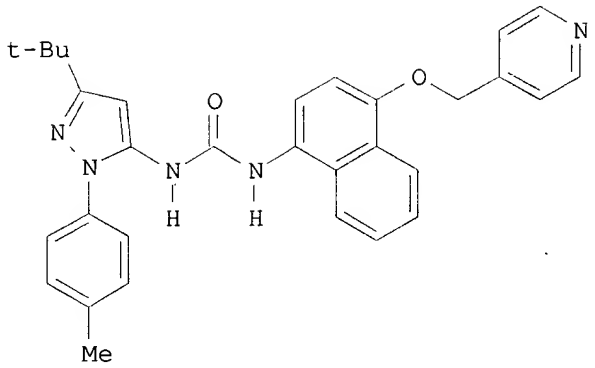

II

AB The title compds. [I; Ar1 = (un)substituted pyrrole, pyrrolidine, pyrazole, etc.; Ar2 = (un)substituted Ph, naphthyl, quinoline, etc.; L = (un)satd. (un)substituted carbon chain wherein one or more methylene groups are optionally replaced by O, N, or S; Q = (un)substituted Ph, naphthyl, pyridinyl, etc.], useful in pharmaceutic compns. for treating diseases or pathol. conditions involving inflammation such as chronic inflammatory diseases, were prepd. E.g., a multi-step synthesis of the urea II was given. Representative compds. I were evaluated and showed IC50 of < 10 .mu.M against TNF prodn. in THP cells.

IT **285983-51-9P 285983-84-8P 285983-87-1P**
285983-96-2P 285983-98-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arom. heterocyclic ureas as antiinflammatory agents)

REFERENCE COUNT: 7
REFERENCE(S):
(1) Bayer Corp; WO 9852558 A 1998 HCAPLUS
(2) Bayer Corp; WO 9932106 A 1999 HCAPLUS
(3) Bayer Corp; WO 9932110 A 1999 HCAPLUS
(4) Bayer Corp; WO 9932111 A 1999 HCAPLUS
(5) Bayer Corp; WO 9932455 A 1999 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:311199 HCAPLUS
DOCUMENT NUMBER: 130:325145
TITLE: Preparation of aromatic heterocyclic compounds as antiinflammatory agents
INVENTOR(S): Regan, John R.; Cirillo, Pier F.; Hickey, Eugene R.; Moss, Neil; Cywin, Charles L.; Pargellis, Christopher; Gilmore, Thomas A.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9923091	A1	19990514	WO 1998-US22907	19981029
W: AU, BG, BR, BY, CA, CN, CZ, HR, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, TR, UA, UZ, VN, YU				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9913675	A1	19990524	AU 1999-13675	19981029
US 6080763	A	20000627	US 1998-181743	19981029
EP 1028953	A1	20000823	EP 1998-957405	19981029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6228881	B1	20010508	US 1999-461446	19991214

PRIORITY APPLN. INFO.: US 1997-64102 P 19971103
US 1998-181743 A3 19981029
WO 1998-US22907 W 19981029

OTHER SOURCE(S): MARPAT 130:325145
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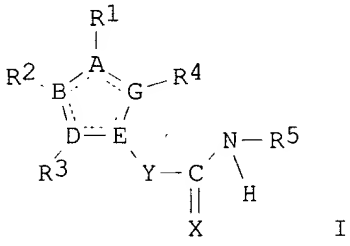

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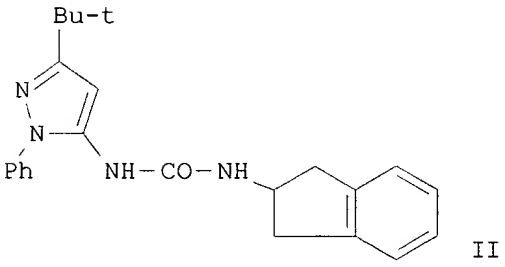

II

AB The title compds. I [A = C, N; B = C, N, O, etc.; D = C, N, S; E = C, N; G = C, S, N; X = S, O, etc.; Y = NH, etc.; R1 = (un)substituted, (partially or fully halogenated) alkyl, etc.; R2 is H, (partially or fully halogenated) alkyl, etc., when B is C or N; R3 is Ph, naphthyl, etc., when D is C or N; or R1R2 = fused Ph or pyridinyl ring; or R2R3 = fused Ph or pyridinyl ring; R4 is H, (partially or fully halogenated) alkyl when G is C or N; R5 is Ph, naphthyl, heteroaryl, etc.] are prepd. I inhibit prodn. of cytokines involved in immunoregulation and inflammation such as

interleukin-1 and tumor necrosis factor. Pyrazole deriv. II was prepd. from phenylhydrazine and 4,4-dimethyl-3-oxopentanenitrile. Compds. of this invention had IC50 < 10 .mu.M against TNF prodn. in an in vitro assay using THP cells.

IT **223724-97-8P 223724-98-9P 223725-00-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arom. heterocyclic compds. as antiinflammatory agents)

REFERENCE COUNT: 3
REFERENCE(S):
(1) Merck & Co Inc; WO 9716442 A 1997 HCAPLUS
(2) Oku, T; US 5624931 A 1997 HCAPLUS
(3) Smithkline Beecham Corporation; WO 9621654 A 1996 HCAPLUS

L8 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:437407 HCAPLUS
DOCUMENT NUMBER: 103:37407
TITLE: Easy synthesis of new ring-fused pyridones from heteroaromatic .beta.-vinylamines
AUTHOR(S): Winters, G.; Sala, A.; De Paoli, A.; Ferri, V.
CORPORATE SOURCE: Res. Lab., DOW-Lepetit, Milan, I-20158, Italy
SOURCE: Synthesis (1984), (12), 1052-4
CODEN: SYNTBF; ISSN: 0039-7881
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 103:37407
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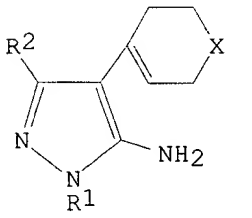

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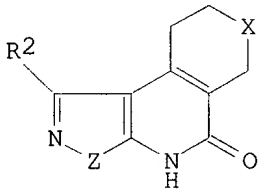

II

AB Cyclization of pyrazoles I (R1, R2 = Me, Ph; X = -, CH2, CH2CH2, NAc, NMe) with RNCO (R = Ph, Et) gave 75-98% cycloalkapyrazolopyridines II (Z = NR1). Similarly prepd. were II (Z = O).

IT **97139-76-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cyclization of)

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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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L9            0 L7

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DICTIONARY FILE UPDATES:   7 NOV 2001  HIGHEST RN 367906-46-5

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HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l7 tot

L7   ANSWER 1 OF 16  REGISTRY  COPYRIGHT 2001 ACS
RN   321850-66-2  REGISTRY
CN   1H-Pyrazole-4-carboxylic acid, 1,3-diphenyl-5-[[(2-
     pyridinylamino)carbonyl]amino]-, methyl ester (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C23 H19 N5 O3
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT
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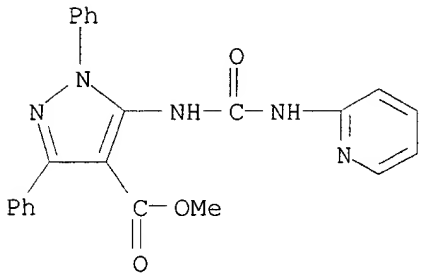

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:131489

L7 ANSWER 2 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 321850-65-1 REGISTRY
CN 1H-Pyrazole-4-carboxylic acid, 5-[[[(4-methoxyphenyl)amino]carbonyl]amino]-1,3-diphenyl-, methyl ester (9CI) (CA INDEX NAME)
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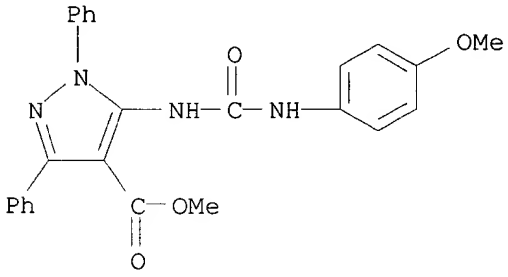
MF C25 H22 N4 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT



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REFERENCE 1: 134:131489

L7 ANSWER 3 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 321850-64-0 REGISTRY
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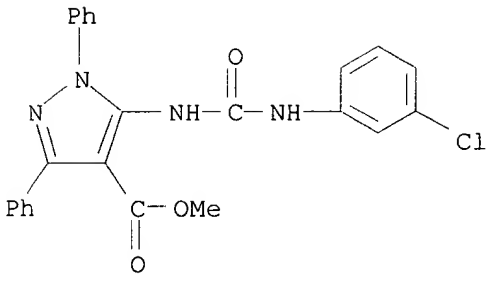
LC STN Files: CA, CAPLUS, CASREACT



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REFERENCE 1: 134:131489

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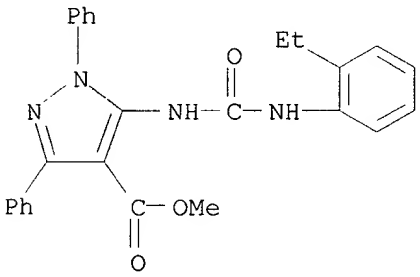
LC STN Files: CA, CAPLUS, CASREACT



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REFERENCE 1: 134:131489

L7 ANSWER 5 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 321850-62-8 REGISTRY
CN 1H-Pyrazole-4-carboxylic acid, 5-[[[(2-methylphenyl)amino]carbonyl]amino]-1,3-diphenyl-, methyl ester (9CI) (CA INDEX NAME)
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MF C25 H22 N4 O3
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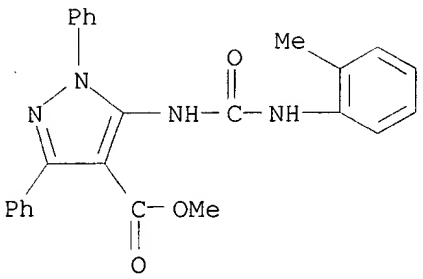
LC STN Files: CA, CAPLUS, CASREACT



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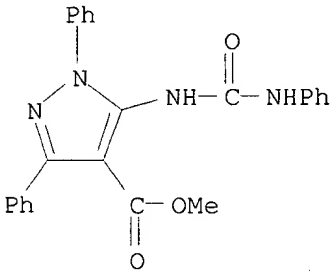
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:131489

L7 ANSWER 6 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 321850-61-7 REGISTRY
CN 1H-Pyrazole-4-carboxylic acid, 1,3-diphenyl-5-[[(phenylamino)carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H20 N4 O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT



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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:131489

L7 ANSWER 7 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 298216-95-2 REGISTRY
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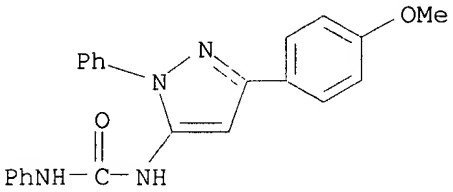
FS 3D CONCORD
MF C23 H20 N4 O2

SR Chemical Library
LC STN Files: CHEMCATS



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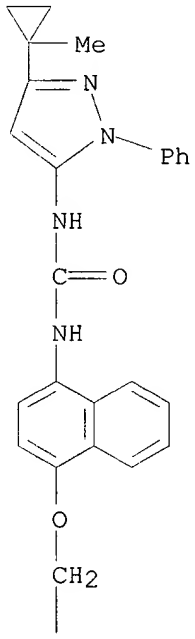
FS 3D CONCORD
MF C30 H33 N5 O3
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



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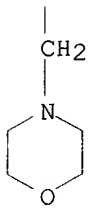

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:120325

L7 ANSWER 9 OF 16 REGISTRY COPYRIGHT 2001 ACS
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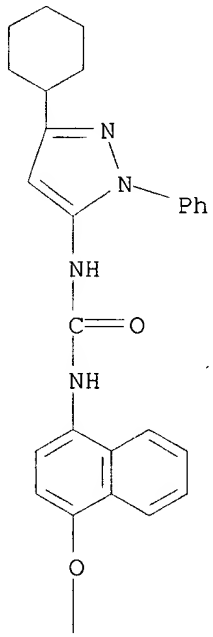
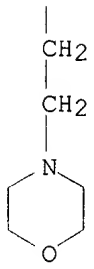
CN Urea, N-(3-cyclohexyl-1-phenyl-1H-pyrazol-5-yl)-N'-[4-[2-(4-morpholinyl)ethoxy]-1-naphthalenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C32 H37 N5 O3
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 2-A



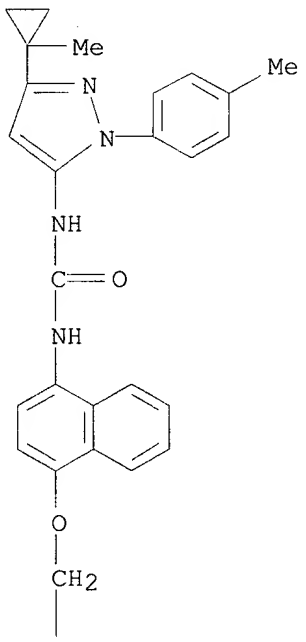
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

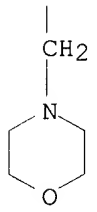
REFERENCE 1: 133:120325

L7 ANSWER 10 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 285983-87-1 REGISTRY
CN Urea, N-[3-(1-methylcyclopropyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]-N'-[4-[2-(4-morpholinyl)ethoxy]-1-naphthalenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H35 N5 O3
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 2-A



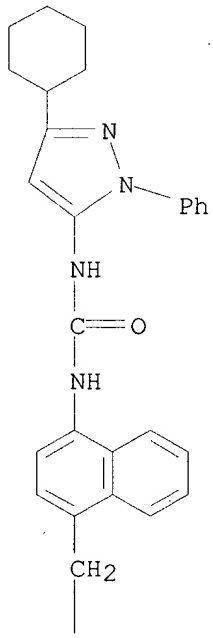
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

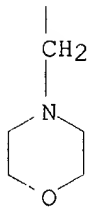
REFERENCE 1: 133:120325

L7 ANSWER 11 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 285983-84-8 REGISTRY
CN Urea, N-(3-cyclohexyl-1-phenyl-1H-pyrazol-5-yl)-N'-[4-[2-(4-morpholinyl)ethyl]-1-naphthalenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C32 H37 N5 O2
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 2-A



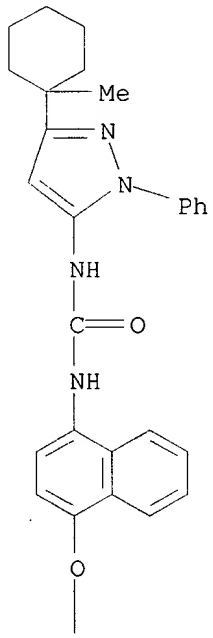
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

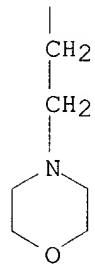
REFERENCE 1: 133:120325

L7 ANSWER 12 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 285983-51-9 REGISTRY
CN Urea, N-[3-(1-methylcyclohexyl)-1-phenyl-1H-pyrazol-5-yl]-N'-[4-[2-(4-morpholinyl)ethoxy]-1-naphthalenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C33 H39 N5 O3
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 2-A

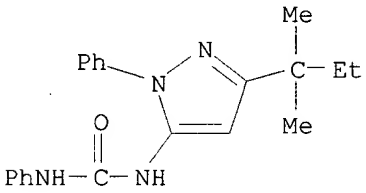


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:120325

L7 ANSWER 13 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 223725-00-6 REGISTRY
CN Urea, N-[3-(1,1-dimethylpropyl)-1-phenyl-1H-pyrazol-5-yl]-N'-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H24 N4 O
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

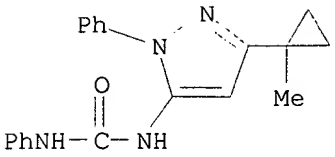


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:325145

L7 ANSWER 14 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 223724-98-9 REGISTRY
CN Urea, N-[3-(1-methylcyclopropyl)-1-phenyl-1H-pyrazol-5-yl]-N'-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C20 H20 N4 O
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

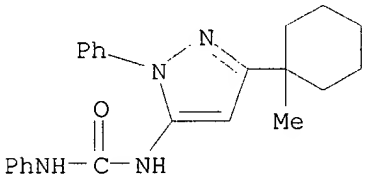


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:325145

L7 ANSWER 15 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 223724-97-8 REGISTRY
CN Urea, N-[3-(1-methylcyclohexyl)-1-phenyl-1H-pyrazol-5-yl]-N'-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H26 N4 O
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

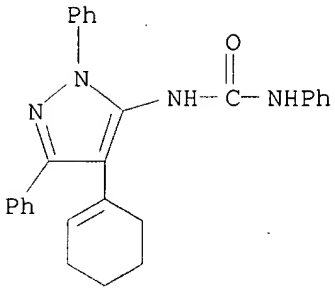


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:325145

L7 ANSWER 16 OF 16 REGISTRY COPYRIGHT 2001 ACS
RN 97139-76-9 REGISTRY
CN Urea, N-[4-(1-cyclohexen-1-yl)-1,3-diphenyl-1H-pyrazol-5-yl]-N'-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H26 N4 O
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 103:37407

my structure search

```
> screen 1006

L11   SCREEN CREATED

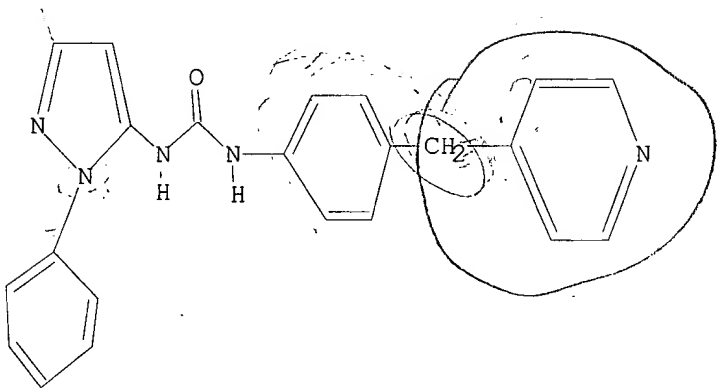
=>
Uploading C:\STNEXP4\QUERIES\urea.str

L12     STRUCTURE UPLOADED

=> que L12 AND L11

L13  QUE L12 AND L11

=> d l13
L13 HAS NO ANSWERS
L11                 SCR 1006
L12                 STR
```




```
Structure attributes must be viewed using STN Express query preparation.
L13                 QUE  ABB=ON  PLU=ON  L12 AND L11


=> s l13
SAMPLE SEARCH INITIATED 17:06:43 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      2 TO ITERATE

100.0% PROCESSED       2 ITERATIONS                              1 ANSWERS
SEARCH TIME: 00.00.01

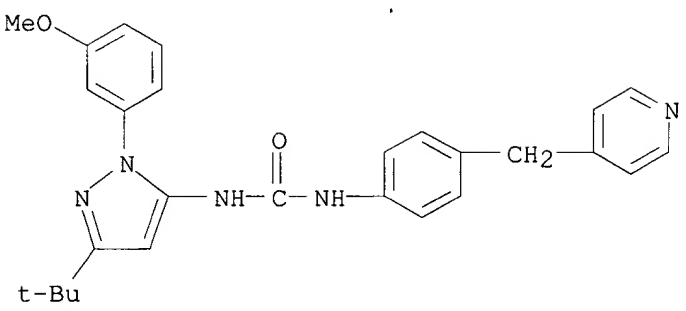
FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            2 TO      124
PROJECTED ANSWERS:               1 TO       80

L14           1 SEA SSS SAM L12 AND L11

=> d l14

L14  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   227623-17-8  REGISTRY
CN   Urea,
N-[3-(1,1-dimethylethyl)-1-(3-methoxyphenyl)-1H-pyrazol-5-yl]-N'-[4-
     (4-pyridinylmethyl)phenyl]- (9CI)  (CA INDEX NAME)
```

FS 3D CONCORD
MF C27 H29 N5 O2
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end

=> screen 1006

L15 SCREEN CREATED

=>
Uploading C:\STNEXP4\QUERIES\urea.str

L16 STRUCTURE UPLOADED

=> que L16 AND L15

L17 QUE L16 AND L15

=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end

=> screen 1006

L18 SCREEN CREATED

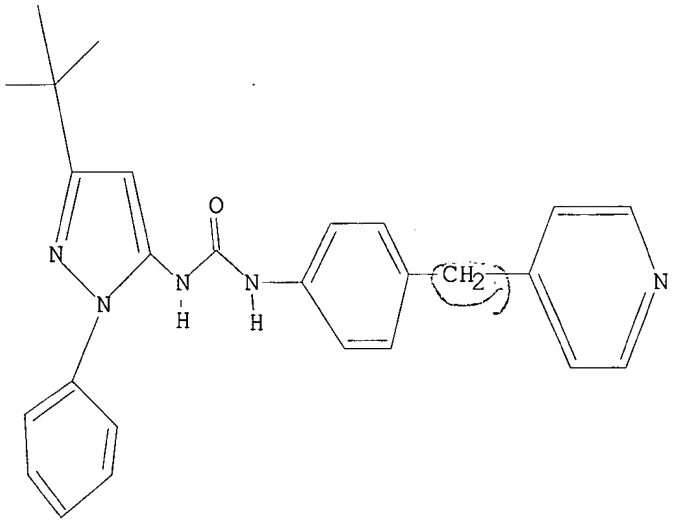
=>
Uploading C:\STNEXP4\QUERIES\urea2.str

L19 STRUCTURE UPLOADED

=> que L19 AND L18

L20 QUE L19 AND L18

=> d l20
L20 HAS NO ANSWERS
L18 . SCR 1006
L19 STR



RN and 456080763/PN

Structure attributes must be viewed using STN Express query preparation.
L20 QUE ABB=ON PLU=ON L19 AND L18

=> s l20
SAMPLE SEARCH INITIATED 17:12:26 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 4 TO ITERATE

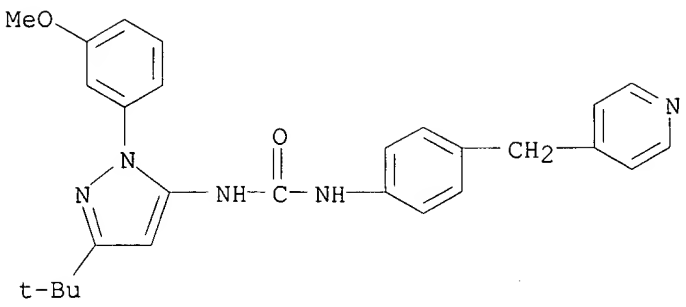
100.0% PROCESSED 4 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS: 4 TO 200
PROJECTED ANSWERS: 1 TO 80

L21 1 SEA SSS SAM L19 AND L18

=> d l21

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN   227623-17-8 REGISTRY
CN   Urea,
N-[3-(1,1-dimethylethyl)-1-(3-methoxyphenyl)-1H-pyrazol-5-yl]-N'-[4-
     (4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS   3D CONCORD
MF   C27 H29 N5 O2
SR   CA
LC   STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

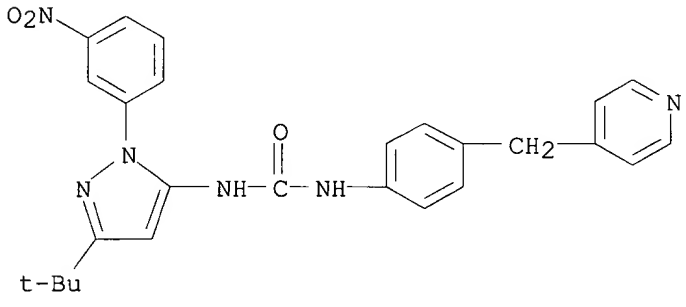
=> s l20 full
FULL SEARCH INITIATED 17:13:49 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 69 TO ITERATE

100.0% PROCESSED 69 ITERATIONS 10 ANSWERS
SEARCH TIME: 00.00.01

L22 10 SEA SSS FUL L19 AND L18

=> d tot

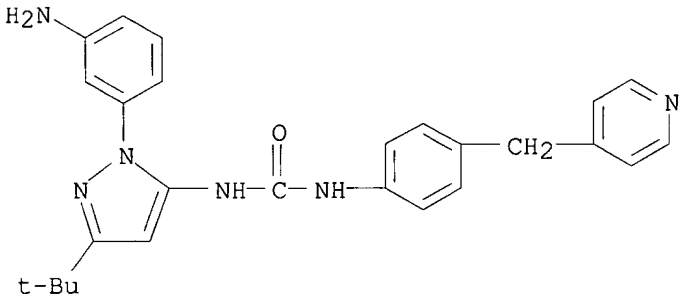
L22 ANSWER 1 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-19-0 REGISTRY
CN Urea,
N-[3-(1,1-dimethylethyl)-1-(3-nitrophenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H26 N6 O3
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

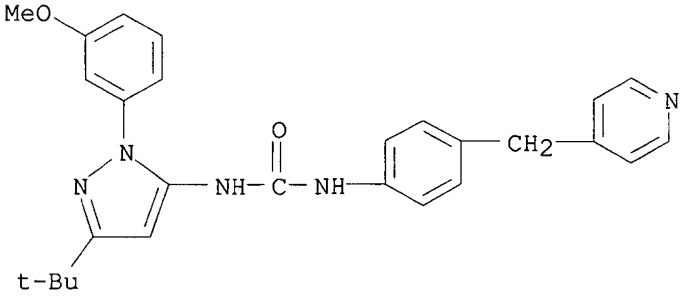
L22 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-18-9 REGISTRY
CN Urea,
N-[1-(3-aminophenyl)-3-(1,1-dimethylethyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H28 N6 O
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

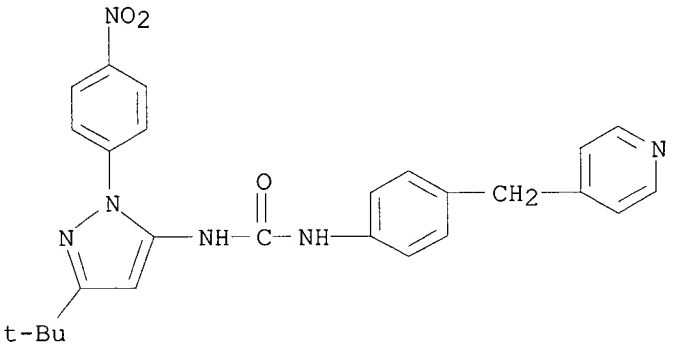
L22 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-17-8 REGISTRY
CN Urea,
N-[3-(1,1-dimethylethyl)-1-(3-methoxyphenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H29 N5 O2
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

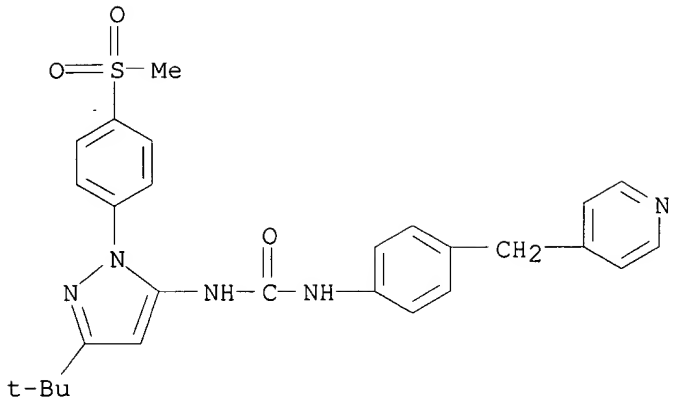
L22 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-16-7 REGISTRY
CN Urea,
N-[3-(1,1-dimethylethyl)-1-(4-nitrophenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H26 N6 O3
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

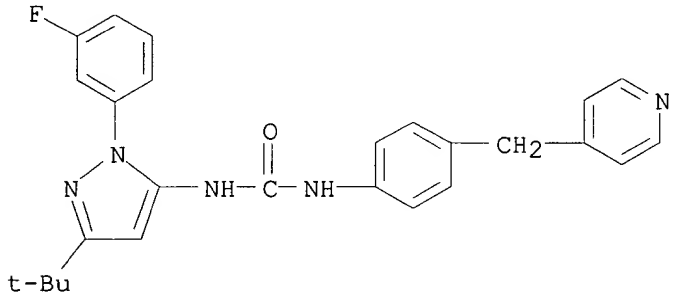
L22 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-15-6 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H29 N5 O3 S
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L22 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-14-5 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-(3-fluorophenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H26 F N5 O
SR CA
LC STN Files: CA, CAPLUS

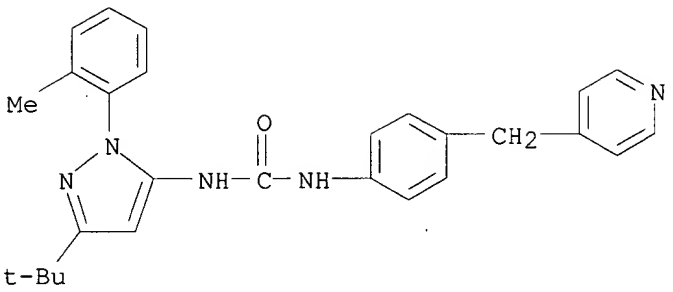


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L22 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-13-4 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-(2-methylphenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H29 N5 O
SR CA

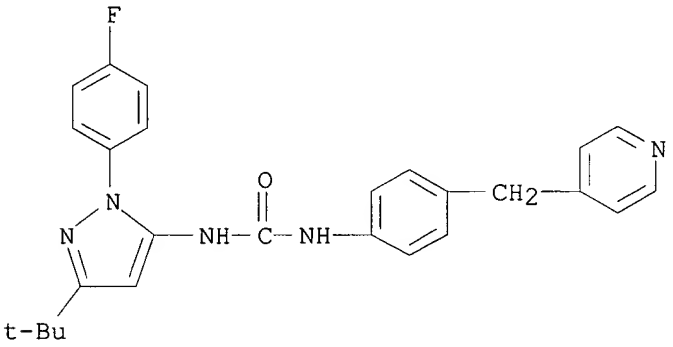
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L22 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-12-3 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H26 F N5 O
SR CA
LC STN Files: CA, CAPLUS

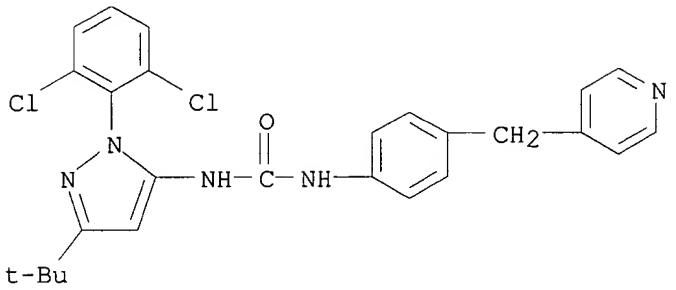


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L22 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-11-2 REGISTRY
CN Urea,
N-[1-(2,6-dichlorophenyl)-3-(1,1-dimethylethyl)-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H25 Cl2 N5 O

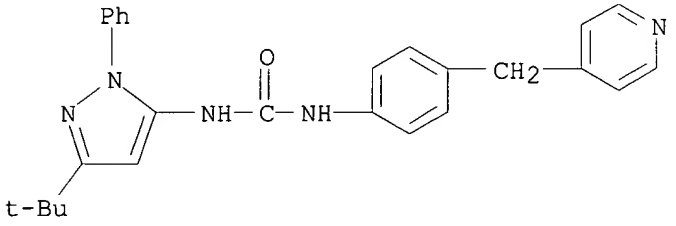
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L22 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2001 ACS
RN 227623-09-8 REGISTRY
CN Urea, N-[3-(1,1-dimethylethyl)-1-phenyl-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethyl)phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H27 N5 O
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	236.29	236.44

FILE 'CAPLUS' ENTERED AT 17:15:26 ON 06 NOV 2001

FILE COVERS 1947 - 6 Nov 2001 VOL 135 ISS 20
FILE LAST UPDATED: 5 Nov 2001 (20011105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

CAplus now provides online access to patents and literature covered in CA from 1947 to the present. On April 22, 2001, bibliographic information and abstracts were added for over 2.2 million references published in CA from 1947 to 1966.

The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.


```
=> s 227623-09-8/rn
             2 227623-09-8
             0 227623-09-8D
L23          2 227623-09-8/RN
                 (227623-09-8 (NOTL) 227623-09-8D )

=> d l23 1-2 AB BIB KWIC

L23  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AB   A method for treatment of p38-mediated disease other than cancer
comprises
     administration of ANHCONHB [I; A = substituted pyrazolyl, thienyl, furyl;
     B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg.
     .gtoreq.1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms].
     Reaction of 2,3-dichlorophenyl isocyanate with
1-(4-methoxyphenyl)-3-tert-
     butyl-5-aminopyrazole in toluene gave title compd. II.  In an in vitro
p38
     kinase assay, I displayed IC50 values of 1-10 .mu.M.
AN   1999:425744  CAPLUS
DN   131:73649
TI   Preparation of pyrazolyl aryl ureas and related compounds as p38 kinase
     inhibitors
IN   Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd;
Scott,
     William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia;
Johnson,
     Jeffrey; Redman, Aniko; Sibley, Robert
PA   Bayer Corporation, USA
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SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9932110	A1	19990701	WO 1998-US26079	19981222
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9919970	A1	19990712	AU 1999-19970	19981222
	EP 1043995	A1	20001018	EP 1998-964708	19981222
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1997-995751	A	19971222		
	WO 1998-US26079	W	19981222		

OS MARPAT 131:73649
RE.CNT 1
RE
(1) Kamata; US 5319099 A 1994 CAPLUS
IT 227622-85-7P 227622-86-8P 227622-87-9P 227622-90-4P 227622-91-5P
227622-92-6P 227622-93-7P 227622-94-8P 227622-95-9P 227622-96-0P
227622-98-2P 227622-99-3P 227623-01-0P 227623-02-1P 227623-03-2P
227623-04-3P 227623-05-4P 227623-06-5P 227623-08-7P
227623-09-8P 227623-10-1P 227623-11-2P 227623-12-3P
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227623-18-9P 227623-19-0P 227623-20-3P 227623-24-7P 227623-25-8P
227623-30-5P 227623-31-6P 228564-94-1P 228564-95-2P 228564-96-3P
228564-97-4P 228564-98-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazolyl aryl ureas and related compds. as p38 kinase inhibitors)

L23 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AB The title compds. ANHCONHB (A = heteroaryl; B = aryl, heteroaryl), raf kinase inhibitors, were prepd. E.g., N-(1-phenyl-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea was prepd.
AN 1999:421660 CAPLUS
DN 131:44811
TI Preparation of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors
IN Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert
PA Bayer Corporation, USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PI   WO 9932455         A1   19990701       WO 1998-US26082  19981222
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             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9919055          A1   19990712       AU 1999-19055    19981222
     EP 1056725          A1   20001206       EP 1998-963810   19981222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     NO 2000003231       A    20000822       NO 2000-3231     20000621
PRAI US 1997-996181      A    19971222
     WO 1998-US26082     W    19981222
OS   MARPAT 131:44811
RE.CNT  1
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(1) Creswell; US 5162360 A 1992 CAPLUS
IT   227622-85-7P   227622-86-8P   227622-87-9P   227622-88-0P   227622-89-1P
     227622-90-4P   227622-91-5P   227622-92-6P   227622-93-7P   227622-94-8P
     227622-95-9P   227622-96-0P   227622-97-1P   227622-98-2P   227622-99-3P
     227623-00-9P   227623-01-0P   227623-02-1P   227623-03-2P   227623-04-3P
     227623-05-4P   227623-06-5P   227623-07-6P   227623-08-7P
     227623-09-8P   227623-10-1P   227623-11-2P   227623-12-3P
     227623-13-4P   227623-14-5P   227623-15-6P   227623-16-7P   227623-17-8P
     227623-18-9P   227623-19-0P   227623-20-3P   227623-21-4P   227623-22-5P
     227623-23-6P   227623-24-7P   227623-25-8P   227623-30-5P   227623-31-6P
     RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic
     preparation); THU (Therapeutic use); BIOL (Biological study); PREP
     (Preparation); USES (Uses)
        (prepn. of aryl- and heteroaryl-substituted heterocyclic ureas as raf
        kinase inhibitors)


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